REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	23.Sep.02	THESIS

4. TITLE AND SUBTITLE
IDENTIFYING PREDICTORS OF ADVERSE DRUG REACTIONS AND ASSOCIATED COSTS USING A CLAIMS DATABASE

5. FUNDING NUMBERS

6. AUTHOR(S)
MAJ REITH CHARLENE H

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
UNIVERSITY OF ARIZONA

8. PERFORMING ORGANIZATION REPORT NUMBER
CI02-698

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
THE DEPARTMENT OF THE AIR FORCE
AFIT/CIA, BLDG 125
2950 P STREET
WPAFB OH 45433

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Unlimited distribution
In Accordance With AFI 35-205/AFIT Sup 1

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

DISTRIBUTION STATEMENT A
Approved for Public Release
Distribution Unlimited

20021017 094

14. SUBJECT TERMS	15. NUMBER OF PAGES
	216
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

MASTER'S / SPECIALIST COMPLETION OF DEGREE REQUIREMENTS

The University of Arizona®
Graduate College
GRADUATE DEGREE CERTIFICATION

Department Pharmaceutical Sciences Date August 7, 2002

Name Charlene Reith Student ID # 470-80-1043

Major Pharmaceutical Sciences

For Departmental Use Only:

Date of Exam 8/13/02 Pass X Fail ____

Satisfied all Departmental Requirements Yes X No ____

Department Head Signature [signature]

THESIS TITLE: Microfilming: Yes ____ No X

Identifying Predictors of Adverse Drug Reactions and Associated Costs Using a Claims Database

CHANGES IN COURSE WORK

Add:	Dept.	Course #	Title	Sem/Yr taken	Units	Grade

Delete:	Dept.	Course #	Title	Sem/Yr taken	Units	Grade

CHANGES IN ADDRESSES: Indicate if change is in current, permanent or diploma address.

COMMITTEE: Print name after signature

JoLaine Draugalis — Chairperson — JoLaine Draugalis — Date 8/13/02

Daniel Malone — Member — Daniel Malone — Date 8/13/02

Edward Armstrong — Edward Armstrong — Date 8/13/02

Rev: 10-98

IDENTIFYING PREDICTORS OF ADVERSE DRUG REACTIONS AND ASSOCIATED COSTS USING A CLAIMS DATABASE

by

Charlene H. Reith

A Thesis Submitted to the Faculty of the

DEPARTMENT OF PHARMACY PRACTICE AND SCIENCE

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE
WITH A MAJOR IN PHARMACEUTICAL SCIENCES

In the Graduate College

UNIVERSITY OF ARIZONA

2002

STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona. Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Charlene Keith

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

JoLaine R. Draugalis, Ph.D.
Professor of Pharmacy Practice and Science

8/20/02
Date

ABSTRACT

Much of the previous adverse drug reaction (ADR) risk-factor analysis was based upon inpatient data. It was postulated that these same risk factors are predictive of ADRs in the ambulatory population. Using medical and pharmacy insurance claims data, three methods were developed to identify potential ADRs. Logistic regression models assessed the association between the risk of an ADR and age, gender, medication use, multiple pharmacies, and chronic disease score (CDS). In adults 18 years of age and older, each risk factor was significantly associated with an ADR risk ($p < 0.001$). Increased medication use had the strongest association ($t = 19.52$, $p < 0.001$). In children, age was negatively associated and number of medications positively associated with an ADR ($p < 0.001$). After controlling for pre-index date expenditures; age, gender, number of medications, and CDS were significantly associated with post-index date expenditures; whereas, the number of pharmacies was not significantly associated with post-index date expenditures.

ACKNOWLEDGEMENTS

I was surrounded by a great number of faculty, peers, and friends willing to share their talents and experiences to make this project take flight. As usual, it is only near the end of the experience that I realize how richly God has blessed me.

My thanks go to the members of my thesis committee, Dr. JoLaine Draugalis, Dr. Ed Armstrong, and Dr. Dan Malone. Time is precious. Their willingness to commit such a valuable resource to help guide this project was appreciated. Their flexibility in arranging their schedules to meet my deadlines went above and beyond my expectations.

The support of the Division of Pharmaceutical Policy and the HOPE Center was invaluable. Dr. Amy Grizzle's willingness to funnel this project to me for a thesis topic and her continued moral and spiritual support throughout were essential to its completion.

Without Rick Rehfeld this project would never have happened, period. His computer programming skills were the foundation for everything that followed. His incredibly calm nature had more influence on me than he will ever know.

The staff at TriWest was extremely patient; my thanks especially to Dr Brian Casull, Denise Boyd, and Gene Lakey for their enthusiastic interest for this research.

My fellow graduate students: Bridget, Cecilia, Sulabha, Durgesh, and Frank, were wonderful. With my family living hundreds of miles away, the value of their friendship, their encouragement, and their empathy were immeasurable. Thanks also to the experienced upperclassmen for sharing the wisdom, and sometimes folly, of their ways in order to make my graduate school experiences easier. The most notable of these was my fellow officer Lt Col (Dr.) David Bennett. I was honored to complete this program with someone of his caliber of integrity and ethic.

I am grateful to my family for never once telling me I was crazy to go back to school fifteen years after completing my undergraduate degree. I know they thought it, but they never said it...I am truly loved!

Without the support of my Air Force family, I would never have been selected for this educational opportunity. The mentors, friends, pharmacists, and technicians I served with are incredible people doing amazing things for the benefit of their patients, the love of their profession, and the good of their country. I pray that I can continue to earn their respect and demonstrate that their confidence in me was well placed.

Although my graduate education was funded by the U.S. Air Force, the views expressed in this thesis are mine and do not reflect the official policy or position of the U.S. Air Force, Department of Defense, or federal government.

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Statement of the Problem

> We study adverse drug effects both qualitatively and quantitatively in order to contribute to more effective pharmacotherapy (Koch-Weser, 1968).

Adverse drug reactions can cause negative patient outcomes, increase healthcare utilization, and contribute to rising healthcare costs. A senior advisor in clinical pharmacology at the National Institutes of Health pointed to several factors contributing to adverse drug reactions; among them was the lack of priority given to studying adverse drug reactions (Atkinson, 2002).

Several studies have attempted to identify risk factors that may be used to predict which patients are most at risk of suffering an adverse drug reaction; however, most of this research has concentrated on adverse drug reactions in hospitalized patients and among hospital admissions, or has been based on theoretical modeling. Little research has been done to determine if the risk factors identified in the literature are applicable to the much larger ambulatory population, nor has there been much work done in developing effective methods of identifying adverse drug reactions in an ambulatory population. Empirical testing in an ambulatory population of these literature-based risk factors needs to occur before intervention plans can be implemented to prevent adverse drug reactions in this population.

The labor intensity and expense of medical record review, as well as privacy issue concerns, severely limit the use of this methodology for researching adverse drug reaction risk factors in the ambulatory population. Medical and pharmacy claims

databases provide data sources for information on ambulatory patients and overcome some of these issues; however, there is limited research using claims data to identify adverse drug reaction risk factors.

There is a national need in healthcare systems to prevent adverse drug reactions when possible. Even if a particular adverse drug reaction were not a preventable one, there is still a legitimate need to track them for several reasons (Bates, 1998). Avoiding the administration of the same medication to the patient who experienced an adverse reaction depends on knowing and documenting the first reaction. Additionally, a reaction that is unpreventable now may be preventable in the future. For example, the development of fexofenadine was spurred by the reports of torsades de pointes caused by terfenadine (Bates, 1998). Prior to the marketing of fexofenadine, clinicians were able to improve their ability to predict which patients were at greater risk of a terfenidine-induced reaction because the adverse drug reaction reports indicated an increased risk with specific classes of interacting drugs. Finally, tracking of adverse drug reactions is now mandated by regulatory agencies.

In order to identify and prevent adverse drug reactions, methods that can accurately predict those most at risk for an adverse drug reaction must be developed. Concurrent with this need, is the need to ensure that the methods developed to identify this sub-population are efficient, practical, and less expensive than current methods.

Purpose of the Study

The primary purpose of this study is to empirically test literature-identified adverse drug reaction risk factors and determine their ability to predict individuals most

at risk for an adverse drug reaction. A secondary purpose of this study is to develop methods to identify individuals experiencing an adverse drug reaction using claims data. Concurrently, this study will collect information on any associated expenditures connected with patients experiencing an adverse drug reaction.

Research Objectives

The following objectives were considered:

Objective 1

Develop methods of detecting adverse drug reactions using medical and pharmacy claims data.

Objective 2

Apply these methods to an existing medical and pharmacy claims database.

Objective 3

Develop predictive mathematical models incorporating literature-identified risk factors for adverse drug reactions.

Objective 4

Test the resultant models' predictive ability on a segment of the medical and pharmacy claims database.

Objective 5

Assess the associated expenditures in those patients identified as experiencing an adverse drug reaction.

Research Questions

It is likely that the method used to detect an adverse drug reaction within a claims database will affect the number and type of adverse drug reactions found. Although claims data have been used to detect potential adverse drug reactions to specific drugs, this study will attempt to use claims data to identify adverse drug reactions in a global sense. The development of a mechanism to identify adverse drug reactions within the claims database comprises the first objective of this thesis. The following research questions apply to objectives one and two.

Question 1

Can adverse drug reactions be detected within a claims database using diagnosis codes specific for adverse drug reactions?

Question 2

Can adverse drug reactions be detected within a claims database using selected drugs and drug-drug combinations as trigger events?

Question 3

Can adverse drug reactions be detected within a claims database using inappropriateness of prescribing criteria as trigger events?

Research Hypotheses

The following hypotheses will be tested if any of the three adverse drug reaction identification methods are successful.

Hypothesis 1

There is no association between age and having an adverse drug reaction.

Hypothesis 2

There is no association between gender and having an adverse drug reaction.

Hypothesis 3

There is no association between the number of medications the patient takes and having an adverse drug reaction.

Hypothesis 4

There is no association between the number of co-morbidities the patient has and having an adverse drug reaction.

Hypothesis 5

There is no association between the number of physicians the patient sees and having an adverse drug reaction.

Hypothesis 6

There is no association between the number of pharmacies the patient uses and having an adverse drug reaction.

Hypothesis 7

There is no difference in expenditures between those identified with an adverse drug reaction and those without an adverse drug reaction.

Definitions

For the purpose of this thesis, the following terms and acronyms are defined.

Adverse drug reaction (ADR): any noxious change in a patient's condition which occurred at dosages normally used in humans, and which a) required treatment, or b) indicated decrease or cessation of therapy with a drug, or c) suggested that future therapy

with the drug carried an unusual risk in this patient (Koch-Weser, 1968; Koch-Weser, Sidel, Sweet, Kanarek, & Eaton, 1969). Medication errors, intentional or accidental overdoses, and therapeutic failures are excluded by this definition.

Adverse drug event (ADE): an injury resulting from medical interventions related to a drug (Bates et al., 1999; Bates, Boyle, Vander Vleit, Schneider, & Leape, 1995). An ADE may result from medication errors or adverse drug reactions. Some researchers will expand this definition to include therapeutic failures and overdoses.

Civilian Health and Medical Program of the Uniformed Services (CHAMPUS): Department of Defense healthcare program that was eventually replaced by the TRICARE Program.

Defense Enrollment Eligibility Reporting System (DEERS): Department of Defense system used to track each beneficiary's status and eligibility for benefits.

Department of Defense (DoD): term used when referring to the military air, land, and ground forces that defend the United States.

International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM): diagnostic coding system required for reporting diagnoses and diseases to all U.S. Public Health Service and Health Care Financing Administration programs for medical service reimbursement.

Military Treatment Facility (MTF): a medical treatment facility, either clinic or hospital, usually located on or very near a military installation. With exception in emergency situations, medical treatment at these facilities is restricted to DoD-eligible beneficiaries.

National Mail Order Pharmacy (NMOP): a point of service for prescription medications available to eligible beneficiaries.

TRICARE: the DoD healthcare program under which medical and pharmacy benefits are supplied to eligible beneficiaries under TRICARE Prime, Extra, or Standard plans for those less than 65 years old and TRICARE For Life for those 65 years and older.

TRICARE Management Activity (TMA): the oversight management office of the TRICARE Program.

CHAPTER 2: REVIEW OF THE LITERATURE

This chapter is a review of the adverse drug reaction-related literature. This review is divided into the following general themes:

1) A review of the factors influencing adverse drug reaction reporting rates;
2) A review of the relevant terminology and classification systems;
3) A review of causality assessment;
4) A review of adverse drug reaction identification methods;
5) A review of adverse drug reaction risk factors;
6) A review of adverse drug reaction associated expenditures;
7) A review of claims database use in research;
8) A review of claims database use in assessing adverse drug reactions; and
9) An overview of the TRICARE insurance plan.

Factors influencing adverse drug reaction reporting rates

The incidence rates of adverse drug reactions vary widely across adverse drug reaction studies. Cooper reported a rate of 15.7 percent adverse drug reaction-associated hospitalizations in a study that examined nursing facility patients in two rural Georgia skilled-nursing facilities (Cooper, 1999). The study population was predominantly old, white, and female. A prospective observation method was used over four years to capture adverse drug reactions. An adverse drug reaction was defined as any unwanted consequence of drug therapy that was given in "...as ordered..." manner, meaning without apparent medication error.

Another study that examined high risk (taking ≥ 5 scheduled medications) ambulatory, older (≥ 65 years) veterans in North Carolina over a 1-year span reported 35 percent of patients experienced adverse drug events (Hanlon et al., 1997). Telephone interviews with the patient were used to obtain most of their information. Adverse drug events were defined as noxious and unintended patient events (i.e., symptoms, signs, or laboratory abnormalities) caused by a medication.

Another study on adverse drug events conducted in a tertiary care center in Utah reported an adverse drug event rate of 1.67 percent (Classen, Pestotnik, Evans, & Burke, 1991). The Utah researchers had patients ranging from 11 years to over 90 years old and obtained their data over an 18-month period with a combination of chart review and patient, physician, and nurse interview. An adverse drug event was defined as "noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions."

Grymonpre and colleagues found 19 percent of hospital admissions were due to drug-related adverse patient events (Grymonpre, Mitenko, Sitar, Aoki, & Montgomery, 1988). This study restricted the population of interest to patients 50 years and older admitted to a tertiary referral center in Manitoba. They obtained data on drug-related adverse patient events (DRAPE) through concurrent medical chart review and patient, family, or healthcare personnel interviews. A DRAPE was defined as any undesired effect associated with drug therapy. A DRAPE could be one or more of these categories: adverse drug reaction, treatment failure, intentional noncompliance, medication error, alcohol-related problem, or other adverse event.

Another study on hospital admissions reported that 5.4 percent of admissions were due to iatrogenic events (Lakshmanan, Hershey, & Breslau, 1986). This group studied iatrogenic disease admissions to a public hospital teaching unit in Cleveland. Their patients ranged in age from 35 to 74. They collected their information through concurrent chart review. Iatrogenic admissions were defined as admissions resulting from adverse reactions to medical therapy, surgery, or diagnostic procedures.

The issues that plague comparisons across the adverse drug reaction studies are evident just within these few studies. Estimates of the frequency of adverse drug reactions varied based upon the study methods, population of interest, and most importantly, by the definition used for an adverse drug reaction.

Even when the studies purportedly were assessing adverse drug reactions under similar scenarios, the frequency rates varied quite dramatically. Studies assessing hospital admissions due to adverse drug reactions reported rates from 0.14 percent to 42 percent (Table 1). Reported frequency rates among outpatient studies ranged from 0.05 percent to 41 percent (Table 2) and among inpatients ranged from 1.6 percent to 23.5 percent (Table 3). As shown in these tables, the data collection methods ranged from spontaneous or voluntary reporting to intense prospective surveillance.

Table 1. Studies assessing hospital admissions due to adverse drug reactions

Frequency (N) Reference	Method **	Setting/Location	Adverse Drug Reaction Definition
2.9 percent (1268) (Hurwitz, 1969a)	2b/3/6	Hospital / Belfast	Any adverse response to medication undesired or unintended by the physician
3.7 percent (7017) (Miller, 1974)	2b/3/6	Hospital / 7-hospital, 3-country Boston Collaborative	Any undesired or unintended effect of a drug
2.9 percent (6063) (Caranasos, Stewart, & Cluff, 1974)	2b/3/6	Teaching hospital / Florida	Unstated
11.1 percent (216) (McKenney & Harrison, 1976)	2/3/4	Teaching hospital / Virginia	Any undesirable or unintended consequence of drug administration
4.1 percent (2499) (Levy, Lipshitz, & Eliakim, 1979)	2/6	General medical ward / Israel	American Registry of Pathology of the Armed Forces Institute of Pathology
12.4 percent (1998) (Williamson & Chopin, 1980)	5	Geriatric hospital / UK	Unstated
5.6 percent (285) (Bergman & Wiholm, 1981)	2b/3/4	University hospital medical wards / Sweden	Based on World Health Organization definition
3.2 percent (906) (Yosselson-Superstine & Weiss, 1982)	2b/3/5	University hospital pediatric admits / Israel	Any undesired or unintended response to medication which may require treatment or alteration of therapy
4.2 percent (834) (Lakshmanan et al., 1986)	2/6	Public teaching hospital / Ohio	Unstated
5.8 percent (293) (Ives, Bentz, & Gwyther, 1987)	2a	Family medicine ward / N. Carolina	Adverse effect of drug product used in accepted therapeutic dose
0.2 percent (3026) *(Mitchell, Lacouture, Sheehan, Kauffman, & Shapiro, 1988)	2/6	Neonatal intensive care unit / 2 teaching, 3 community hospitals / U.S.	An unintended or undesired effect of a drug
22 percent (725) *(Mitchell et al., 1988)	2/6	Children's' cancer ward / same location as above	An unintended or undesired effect of a drug
2 percent (6546) *(Mitchell et al., 1988)	2/6	Pediatric admits / same location as above	An unintended or undesired effect of a drug
11.6 percent (718) (Grymonpre et al., 1988)	2b/3/6	Tertiary referral center / Canada	Based on World Health Organization definition
9.4 percent (244) (Colt & Shapiro, 1989)	2a	Teaching hospital / Pennsylvania	Any undesired or unintended response to a med that occurs despite its use at the appropriate dosage for prophylaxis, diagnosis, or therapy
16.8 percent (315) (Col, Fanale, & Kronholm, 1990)	2/3	Teaching hospital / Massachusetts	Undesirable clinical manifestation that is consequent to and caused by the administration of a particular drug
1.1 percent (48678) (Ibanez, Laporte, & Carne, 1991)	2/3/4	University hospital / Spain	Based on World Health Organization definition

Table 1. Studies assessing hospital admissions due to adverse drug reactions (continued)

1.6 percent (5623) (Larmour et al., 1991)	2/6	Teaching hospital / Australia	Augmented World Health Organization definition
7.9 percent (1999) (Hallas et al., 1992)	2b/3/6	Medicine ward / Denmark	Unintended and undesirable effect of a drug
0.14 percent (10184) (Prince, Goetz, Rihn, & Olsky, 1992)	2a	Tertiary care hospital / Pennsylvania	Unstated
2.7 percent (965) (Dartnell et al., 1996)	2b/3	Teaching hospital / Australia	Based on World Health Organization definition
5.3 percent (452) (Nelson & Talbert, 1996)	2b/6	University hospital ICU and internal medicine / Texas	Unstated
42 percent (106) (Mannesse, Derkx, deRidder, Man in't Veld, & van der Cammen, 1997)	2/3	Medical wards / Netherlands	Unstated
24.8 percent (153) (Azaz-Livshits et al., 1998)	2/4	Medical ward / Israel	Unstated
3 percent (329) (Moore, Lecointre, Noblet, & Mabille, 1998)	5	Hospital / France	Unstated
0.6 percent (1682) (Easton, Parsons, Starr, & Brien, 1998)	2b/3	Children's' hospital / Australia	Any response to a drug that is undesired, unintended or unexpected in doses recognized in accepted medical practice
15.7 percent (332) (Cooper, 1999)	2b	Hospital admits from two skilled-nursing facilities / Georgia	Any unwanted consequence of drug therapy that was given in as ordered manner, that is, no error
7.5 percent (200) (Green, Mottram, Rowe, & Pirmohamed, 2000)	2/3/6	Acute medical assessment unit / UK	Based on World Health Organization definition
21.4 percent (444) (Lagnaoui, Moore, Fach, Longy-Boursier, & Begaud, 2000)	5	Internal medicine unit / France	Clinical or biological abnormality associated with the use of a drug
12 percent (106) (Mannesse, Derkx, deRidder, Man In 'T Veld', & van der Cammen, 2000)	2/3	University hospital / Netherlands	Undesirable clinical manifestation consequent to and caused by the administration of a particular drug or interacting drugs, excluding intentional overdose, substance abuse, and therapeutic failure
31.9 percent (3137) (Pouyanne, Haramburu, Imbs, & Begaud, 2000)	5	Medical ward of 33 teaching and general hospitals / France	Based on World Health Organization definition

* Same study but different groups assessed ** Methods used in data collection
1 spontaneous/voluntary reporting 2 chart review 2a retrospective chart review 2b prospective chart review
3 patient survey or interview 4 screening 5 prospective surveillance 6 health professional interview

Table 2. Studies assessing outpatient occurrence of adverse drug reactions

Frequency (N) Reference	Method **	Setting/Location	Adverse Drug Reaction Definition
36 percent (749) (Meleney & Fraser, 1969)	2a/3	Outpatients at University of Florida hospital	Unstated
31.5 percent (200) (Kellaway & McCrae, 1973)	3	Discharges from Auckland Hospital / New Zealand	Based on World Health Organization definition
2 percent (9315) (Mulroy, 1973)	5	General practice / UK	Any adverse reaction to medication undesired or unintended by the physician
41 percent (817) (Martys, 1979)	3	General practice / UK	World Health Organization definition and any unintended or undesired consequence of drug therapy
30 percent (299) (Klein, German, Levine, Feroli, & Ardery, 1984)	3	General medicine clinics / Maryland	Unstated
11.1 percent (4244 courses) (Kramer et al., 1985)	2b/3	General pediatric group / Canada	Undesirable clinical manifestation consequent to and caused by the administration of a particular drug
4.8 percent (1026) (Hutchinson, Flegel, Kramer, Leduc, & Ho Ping Kong, 1986)	3	Internal medicine group practice / Canada	Unstated
1.7 percent (36740) (Lumley, Walker, Hall, Staunton, & Grob, 1986)	1/5	General practice / UK	Based on World Health Organization definition
10 percent (3170) (Chrischilles, Segar, & Wallace, 1992)	3	Community survey / Iowa	Unstated
21 percent (463) (Koecheler Schneider, Mion, & Frengley, 1992)	2a	Geriatric and general medicine clinic / Ohio	Based on World Health Organization definition
0.67 percent (10184) (Prince et al., 1992)	2a	Emergency department visits / Pennsylvania	Unstated
0.86 percent (13703) (Stoukides, D'Agostino, & Kaufman, 1993)	2	Emergency department / Rhode Island	Unstated
Unstated (Unstated) (Finn & Carlstedt, 1995)	1/2/3/6	General medicine practice / Indiana	Unstated
1.3 percent (1260) (Dennehy, Kishi, & Louie, 1996)	2a	Emergency department visits to teaching hospital / California	Any drug-related illness that was noxious and unintended or that occurred as a result of a medical intervention related to a drug
1.3 percent (62216) (Schneitman McIntire, Farnen, Gordon, Chan, & Toy, 1996)	2a/3	Health maintenance organization emergency department / California	Unstated

Table 2. Studies assessing outpatient occurrence of adverse drug reactions (continued)

35 percent (167) (Hanlon et al., 1997)	2a/3	Veterans Administration general medicine clinic / North Carolina	Noxious and unintended patient events (i.e., symptoms, signs, or laboratory abnormalities) caused by a drug
5.7/yr (2185) (Veehof, Stewart, Meyboom-de Jong, & Haaijer-Ruskamp, 1999)	2a/4	Three general practices / Netherlands	Adverse effects observed and registered by physicians
20.3 percent (256) (Gray, Mahoney, & Blough, 1999)	3	Three home health agencies / Wisconsin	Unstated
14.2 percent (253) (Tafreshi, Melby, Kaback, & Nord, 1999)	2b/3	Emergency department visits in tertiary referral hospital / Arizona	Any undesirable, unintended, and unexpected event that requires discontinuing a drug, modifying a dose, prolonging hospitalization, or providing supportive treatment (add DDI)
1.5 percent (7890) (Menniti-Ippolito, Raschetti, Da Cas, Giaquinto, & Cantarutti, 2000)	5	Pediatrician offices / Italy	Unstated
2.8 percent (2248) *(Gandhi et al., 2000)	2a	11 general internal medicine practices / Massachusetts	Unstated
17.5 percent (2248) *(Gandhi et al., 2000)	3	11 general internal medicine practices / Massachusetts	Unstated
0.05 percent (28530) (Lacoste-Roussillon, Pouyanne, Haramburu, Miremoint, & Begaud, 2001)	5	General practice / France	Based on World Health Organization definition
0.4 percent (7540) (Letrilliart et al., 2001)	1/5	Post-discharge in general practice / France	Augmented World Health Organization definition
1.7 percent (16253) (Millar, 2001)	1/2a	Rural general practice / Scotland	Augmented World Health Organization definition
2.6 percent (4764) (Malhotra, Jain, & Pandhi, 2001)	2/3/5	Emergency department of tertiary care hospital / India	Based on World Health Organization definition

* Same study but different methods ** Methods used in data collection
1 spontaneous/voluntary reporting 2 chart review 2a retrospective chart review 2b prospective chart review
3 patient survey or interview 4 screening 5 prospective surveillance 6 health professional interview

Table 3. Studies assessing inpatient occurrence of adverse drug reactions

Frequency (N) Reference	Method **	Setting/Location	Adverse Drug Reaction Definition
10.8 percent (900) (Smith, Seidl, & Cluff, 1966)	5	Medical ward / Florida	Any response of a patient to a drug that was unintended and undesired by the prescribing physician
10.2 percent (1160) (Hurwitz & Wade, 1969)	2b/3/6	7 general wards & 1 psych hospital / Belfast	Any adverse response to medication undesired or unintended by the physician
10.6 percent (658) (McKenzie, Stewart, Weiss, & Cluff, 1973)	2b/4/6	Pediatric ward teaching hospital / Florida	Any undesired or unintended response to medication which may require treatment or alteration of therapy
23.5 percent (170) (Gray, Adams, & Fallon, 1973)	5	Medical ward / North Carolina	Based on World Health Organization definition
18 percent (521) (Leach & Roy, 1986)	2b/3/4	Geriatric ward / UK	Based on World Health Organization definition
1.76 percent (36653) (Classen et al., 1991)	2b/3/4/6	Teaching hospital / Utah	Based on World Health Organization definition
5.8 percent (9148) (Carbonin, Pahor, Bernabei, & Sgadari, 1991)	1/2b	Medical and geriatric wards / multicenter / Italy	Based on World Health Organization definition
8.8 percent (160) *(Schumock, Thornton, & Witte, 1991)	5	Teaching hospital / Illinois	Reaction requiring a major change in patient management
2.5 percent (160) *(Schumock et al., 1991)	2a	Teaching hospital / Illinois	Reaction requiring a major change in patient management
6.4 percent (329) (Moore et al., 1998)	5	General medicine ward / France	Unstated
16.6 percent (409) (Martinez-Mir et al., 1999)	2/3/5	Pediatric hospital / Spain	Based on World Health Organization definition
4.7 percent (444) (Lagnaoui et al., 2000)	5	Internal medicine unit admits/France	Clinical or biological abnormality associated with the use of a drug
1.6 percent (9311) (Suh, Woodall, Shin, & Hermes-De Santis, 2000)	1/2	University hospital / New Jersey	Based on World Health Organization definition
2 percent (16916) (Bordet, Gautier, LeLouet, DuPuis, & Caron, 2001)	1	Cardiology hospital / France	Noxious or unintended events occurring at therapeutic doses and inducing changes in foreseeable clinical outcomes

* Same study but different methods ** Methods used in data collection
1 spontaneous/voluntary reporting 2 chart review 2a retrospective chart review 2b prospective chart review
3 patient survey or interview 4 screening 5 prospective surveillance 6 health professional interview

Even when the methods of data collection were the same, however, the results varied based upon the population of interest. Mitchell's group used the same methods of data collection but applied them to neonatal intensive care unit admissions, pediatric ward admissions, and children's cancer ward admissions (Mitchell et al., 1988). They reported an adverse drug reaction frequency of 0.2, 2, and 22 percent, respectively. The higher frequency in the pediatric oncology patients as compared to the pediatric ward patients was expected since the drugs used to treat the cancer patients have higher toxicity levels that subsequently increase the risk for an adverse drug reaction.

Perhaps the most important reason behind the disparity among studies is the difference in the definition used for an adverse drug reaction. Regulatory agencies mandate that institutional health care facilities have a definition of an adverse drug reaction and a mechanism to report them. They do not mandate what the definition should be but merely that all practitioners in the institution be familiar with the definition (Ninno & Ninno, 2002). Although attempts at standardization have been made, the literature is still rife with studies that incorrectly interchanged the terms adverse drug events, adverse drug reactions, and medication errors. The next section will review these terms as well as other related terminology.

Relevant terminology and classification systems

The problem of defining, classifying, and describing adverse drug reactions is not new. As moderator of a symposium on adverse drug reactions, Dr Jan Koch-Weser began the proceedings with this statement.

> So difficult has it been to define an adverse drug reaction to everybody's satisfaction that occasional impatience with the problem is apparent. Some have urged us to leave this question to the common sense of all concerned. Not only is this a bizarre approach to scientific investigation, but it has not worked in practice. Various sensible and experienced groups are using the term "adverse drug reaction" to describe entirely different bodies of phenomena. These are not minor differences; according to the definition used the number of events studied by two such groups may differ by orders of magnitude. It has also been suggested that no consensus on what constitutes an adverse drug reaction can ever be reached because the interests and motivations of drug producers, investigators and regulators are too diverse. This argument has no merit since all of us are primarily concerned with the advancement of knowledge in this crucial area.
>
> Useful information concerning the nature and incidence of adverse drug reactions can be and has been developed by studies using almost any definition. Why then is it so desirable to come to some common understanding of what is meant by an adverse drug reaction? The answer lies in the obvious need for collaboration in this area. Comparison and merging of results from many groups studying adverse drug reactions in this and other countries may well be a *sine qua non* of rapid and significant advances in our quantitative knowledge. Any valid comparison and, even more, any merging of data from studies using entirely different definitions are difficult or impossible. All statements concerning incidence of adverse drug reactions are functions of the definition used (Koch-Weser, 1968).

Over 30 years later, the disparity of definitions remains. A 1986 survey of adverse drug reaction reporting programs found 59 different definitions for an adverse drug reaction being used among 76 hospitals surveyed (Case & Guzzetti, 1986). There was a better concurrence of definitions among 66 Veterans Administration (VA) facilities surveyed (Corr & Stoller, 1996). Many of the surveyed hospitals in both studies cited the World Health Organization's definition.

The World Health Organization (WHO) defined an adverse drug reaction as "any response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for modification of physiologic function" (World Health Organization, 1970).

Several issues with the WHO terminology were raised (Edwards & Aronson, 2000). First, the definition excluded error as a source of adverse effects. Second, the term noxious was vague and raised the question of whether it included all adverse reactions, no matter how minor. Lastly, by the definition's use of the word drug, it excluded reactions due to contaminants or inactive excipients in the formulation and thus the use of the word drug might be better replaced with the more inclusive word medicinal.

Koch-Weser provided one of the earliest and more operationally useful definitions of adverse drug reactions (Koch-Weser, 1968). The definition of an adverse drug reaction was: "any noxious change in a patient's condition which a physician believes to be due to a drug, which occurs at dosages normally used in man, and which 1) requires treatment, or 2) indicates decrease or cessation of therapy with the drug, or 3) suggests that future therapy with the drug carries an unusual risk in this patient." This definition, in combination with the WHO definition, appeared to be the framework for the American Society of Health-System Pharmacists' (ASHP) (1998) draft recommendations.

The ASHP draft suggested that an adverse drug reaction was any unexpected, unintended, undesired, or excessive response to a medicine that

a) requires discontinuing the medicine (therapeutic or diagnostic);

b) requires changing the medication therapy;

c) requires modifying the dose (except for minor dosage adjustments);

d) necessitates admission to a hospital;

e) prolongs stay in a health care facility;

f) necessitates supportive treatment;

g) significantly complicates diagnosis;

h) negatively affects prognosis; or

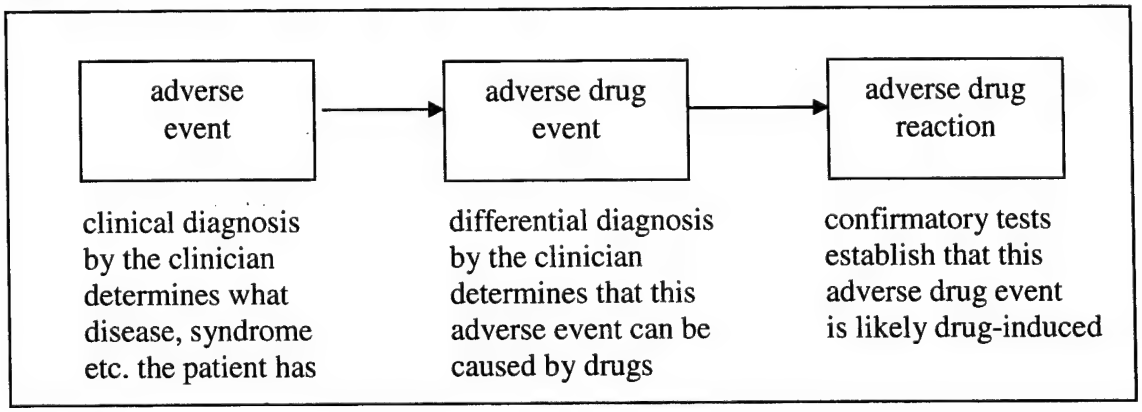
i) results in temporary or permanent harm, disability, or death.

This definition further operationalized the more nebulous definition by the WHO; however, it contrasted rather sharply with other definitions (Gandhi, Seger, & Bates, 2000). Gandhi's group. limited their interpretation of adverse drug reactions to non-preventable adverse drug events in which an injury occurred but no error. Since identification of errors held the greatest interest from their prevention aspect, they used the term adverse drug event in order to expand their study's definition. The term adverse drug event was seen throughout the literature and was also defined in several ways. Edwards and Aronson stated that the difference between adverse drug reaction and adverse drug event was based upon viewpoint (Edwards & Aronson, 2000). An adverse drug reaction was an adverse outcome that could be attributed to some action of a drug, whereas an adverse drug event was an adverse outcome that occurred while a patient was taking a drug but was not necessarily attributed to it.

Pirmohamed and colleagues concurred, but with a slight variation, stating that "an adverse drug reaction is any undesirable effect of a drug beyond its anticipated

therapeutic effects occurring during clinical use but an adverse drug event is an untoward occurrence after exposure to a drug that is not necessarily caused by the drug" (Pirmohamed, Breckenridge, Kitteringham, & Park, 1998). This viewpoint was supported by the WHO's definition of adverse drug event which is "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (WHO Collaborating Centre for International Drug Monitoring, 2002). Naranjo followed this by stating that an adverse drug event was only referred to as an adverse drug reaction when a causal relationship was confirmed. Naranjo proposed the pathway in Figure 1 (Naranjo, Shear, & Lanctot, 1992).

Figure 1. Adverse event to adverse drug reaction (Naranjo et al., 1992)



For example, a clinical diagnosis of a gastrointestinal bleed would be considered an adverse event. The differential diagnosis for the cause of the bleed includes peptic ulcer, Crohn's disease, alcoholism, and medication use as well as a number of other causes. The inclusion of medications as a potential cause would classify this as an

adverse drug event. As alternative causes are ruled out and a causal link established between a suspect drug and the event, the adverse drug event moves into the adverse drug reaction category. For example, if the physician determined the bleed was caused by an ibuprofen-induced ulceration of the stomach, then this could be classified as an adverse drug reaction. A medication error or an overdose, however, would remain classified as an adverse drug event.

Results from the Harvard Medical Practice Study II were frequently cited in adverse drug reaction studies. This study looked at adverse events among 30,195 randomly selected records. The study defined adverse events as "an unintended injury that was caused by medical management and that resulted in measurable disability" (Leape et al., 1991). One of 15 categories of adverse events was drug complications. Drug complications were reported as the most common single type of adverse event; yet, when the authors described the events that were included in the drug complication category, the components included both medication errors and adverse drug reactions. This distinction was not always clarified when these results were cited in other studies. This inaccuracy demonstrates the need for caution when comparing study results.

The interplay among the terms of medication error, adverse drug event, and adverse drug reaction is easily the largest source of confusion in the adverse drug reaction literature. Bates and colleagues defined medication errors as errors in the process of ordering or delivering medication (Bates et al., 1995). An injury or potential for injury need not be present to classify as a medication error but some medication errors did result in adverse drug events, that is, injury. In their studies, adverse drug events were defined

as injuries resulting from medical intervention related to a drug. Adverse drug events are comprised of either medication errors or from adverse drug reactions. Studies reporting on adverse drug events, as well as studies citing these results, did not consistently differentiate between errors and adverse drug reactions.

Adverse drug events can result from medication errors or adverse drug reactions. For the most part, the studies published using the term adverse drug events defined the term as an injury resulting from medical interventions related to a drug: consistent with the WHO definition (Bates, Leape, & Petrycki, 1993; Brennan et al., 1991; Cullen et al., 1997; Field et al., 2001). Unfortunately, one of the key studies that tried to empirically assess the morbidity, mortality, and additional costs attributable to adverse drug reactions misused the terms (Classen, Pestotnik, Evans, Lloyd, & Burke, 1997). The author stated use of the WHO definition of an adverse drug event but then quoted the WHO definition for adverse drug reaction; perpetuating the confusion between the terms.

A distinction between a side effect and an adverse drug reaction was also made by some researchers. Acknowledging that the line between an accepted undesirable side effect and an unexpected significant reaction that might influence a therapeutic decision was rarely clear-cut, Koch-Weser suggested that the reviewer determine whether the effect indicated or resulted in a change of therapy (Koch-Weser, 1968). This change in therapy could be either cessation of the drug(s), reduction in dosage, or treatment to counteract the reaction. If the reaction were deemed important enough to make future therapy with that drug inadvisable in that patient, it was also considered an adverse drug

reaction. It would not be considered an adverse drug reaction if the drug were used in an inappropriate manner.

Another difference between adverse drug events and reactions is that of therapeutic failures, drug withdrawal, drug abuse, and drug overdose. Some authors excluded failure to accomplish the intended purpose from their definition of adverse drug reactions (Karch & Lasagna, 1975). While Karch and Lasagna interpreted the WHO's definition of an adverse drug reaction as including therapeutic failures, they contended that the failure of a drug to produce a desired effect is distinctly different from the production of an undesirable effect and should not be lumped in with adverse drug reactions. Others specifically included lack of effect when discussing varying degrees of adverse drug reactions (Fincham, 1991). Fincham's intention for including lack of effect appeared to be restricted to a lack of effect secondary to drug-drug, drug-food, or drug-lifestyle interactions rather than outright therapeutic failures. Meyboom argued most convincingly for the inclusion of therapeutic ineffectiveness as an adverse drug reaction maintaining that these types of reports were important in detecting pharmaceutical defects, interactions, inappropriate use, resistance, tolerance, short term effectiveness, and unsustained effectiveness (Meyboom, Lindquist, Flygare, Biriell, & Edwards, 2000). Researchers concurred that the WHO definition already excluded intentional or accidental poisoning and drug abuse (American Society of Health-System Pharmacists, 1998; Brown & Landry, 2001; Karch & Lasagna, 1975).

The more global term of drug-related problems was used in an oft cited study on the costs of drug-related morbidity and mortality (Johnson & Bootman, 1995). The term

drug-related problems encompassed adverse drug reactions, drug interactions, and overdosage along with five other problems related to lack of proper drug therapy or failure to supply drug therapy when indicated.

Typically, adverse drug reactions have been divided into two major categories (Moore, 2001). Type A reactions or augmented reactions were dose-dependent and could be found in susceptible patients at therapeutic doses and in most patients as dosage increased. Moore purports that Type A reactions could be observed in as many as 25 percent to 40 percent of patients or up to 100 percent for anti-cancer drugs. Because these reactions were dose dependent, they potentially could be avoided, but because they were so common, they were rarely reported. Indeed, insisting that they be routinely reported could clog the reporting systems with trivial information; yet, if these reactions were resulting in emergency department visits, hospitalizations, physician office visits, and additional prescriptions to compensate for adverse reactions, a case could be made that there is a not so trivial cost to the patient and to society.

The second category of adverse drug reactions was Type B or bizarre. Type B reactions were the rare, idiosyncratic reactions that were generally spontaneously reported because they were more spectacular. These reaction types were often highly visible and could lead to removal of the drug from the market even though their incidence was very low.

Although Type A and Type B adverse reactions were the most commonly seen categories in the literature, some experts expanded the categories to include Type C and Type D reactions (Royer, 1997). Continuous long term effects or Type C reactions were

those that were expected in a treated population but had an increase in frequency that manifested as increased rates of spontaneous disease. Oftentimes this type of reaction was a disagreeable discovery in studies designed to detect something else. Royer described Type C reactions as those that were the result of adaptive changes to the drug or the development of tolerance to an addictive drug. Some examples of this would include the tardive dyskinesias caused by some neuroleptics or the rebound hypertension experienced after the discontinuation of some of the antihypertensive medications.

Type D or delayed reactions were described as transitory and hidden defects of life essential pathways. Type D reactions would include those due to the gene toxicity of some drugs, whether mutagenic, carcinogenic, or teratogenic. A common example of this would be the adenocarcinoma that occurred in daughters of women who took diethylstilbestrol during pregnancy.

While the expanded categories were more descriptive, most of the literature placed Type A, C, and D reactions within a single category. Type B reactions were non-dose related with an immunologic response that made them distinctly different from the other types. A further distinction between Type A and Type B reactions was that Type B reactions tended to be associated with a higher mortality and lower morbidity profile, whereas, Type A reactions tended to have a higher morbidity but a lower mortality profile. It must also be noted that the reactions captured as an inpatient are generally the acute effects of the drug while those that occur only after long-term treatment are not commonly detected in the hospital setting (Nolan & O'Malley, 1988).

Other classification schemes were used to assess the strength of association between the drug and the reaction or the level of severity. Causality (did the drug do it?) issues should be addressed in any study on adverse drug reactions; yet, many of the manifestations of adverse drug reactions are nonspecific and confounded by the administration of multiple drugs. Establishing that the drug rather than the disease progression or some other patient-related factor caused the adverse reaction was difficult and often debated. The issue of causality ultimately affects whether an adverse drug reaction is reported. The differing techniques used to assess causality contributed to the variation in reported adverse drug reaction frequency rates.

Causality assessment

The classification schemes used in the adverse drug reaction literature varied on which levels of adverse drug reactions were collected and reported. While some studies reported all classifications, others only reported those reactions that were definite or probable, and still others offered no assessment of causality. This section describes some causality terminology and discusses several classification methods found in the literature.

The WHO provided a causality assessment of suspected adverse drug reactions. This range of causality classifications included the following scope of terms (Edwards & Aronson, 2000; Karch & Lasagna, 1975).

1) *Certain* adverse drug reactions were those that included a clinical event with confirmatory laboratory test abnormalities that could not be explained by the concurrent disease or other drugs/chemicals, occurred in a plausible time relation to drug administration, improved upon stopping the drug

(dechallenge), and resulted in a similar response upon rechallenge with the drug.

2) *Probable or likely* adverse drug reactions were similar to those in the certain classification with the exception that rechallenge was not required to fulfill this definition.

3) *Possible* adverse drug reactions were clinical events, including laboratory test abnormalities, with a reasonable temporal relation to the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.

4) *Unlikely* adverse drug reactions were clinical events with a temporal relation to drug administration that made a causal relation improbable and in which other drugs, chemicals, or underlying diseases provided a plausible explanation.

5) *Conditional or unclassified* adverse drug reactions were reported events when more data were essential for a proper assessment or the data were still being examined.

6) *Unassessable or unclassifiable* adverse drug reactions were reported events suggesting an adverse reaction that could not be judged because information was insufficient or contradictory and could not be supplemented or verified.

Some authors collapsed the last three categories to conditional and doubtful, while others classified all reactions into possibly related, probably related, not related, and unclassified (Karch & Lasagna, 1975). More commonly, the six categories were

collapsed to just four: definite, probable, possible, or doubtful. In this instance the terms were defined as follows (Naranjo et al., 1981).

1) *Definite* adverse drug reactions followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, followed a recognized response to a suspected drug, were confirmed by improvement on withdrawing the drug, and reappeared on re-exposure.
2) *Probable* adverse drug reactions followed a reasonable temporal sequence to the suspected drug, were confirmed by withdrawal but not by re-exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.
3) *Possible* adverse drug reactions followed a temporal sequence after a drug, possibly followed a recognized pattern to the suspected drug, or could be explained by characteristics of the patient's disease.
4) *Doubtful* adverse drug reactions were likely related to factors other than a drug.

The classifications also varied by country. A review of the causality terms used at national pharmacovigilance centers in 10 European countries found each country had different categorizations ranging from four to six categories of causality (Venulet & Ten Ham, 1996).

Regardless of the classification system used the fundamental problem remains establishing a cause-effect relationship between the drug and reaction. Auriche and Loupi stated that objective proof that a reaction was caused by a particular drug was the

exception insisting that "as a rule, it is a matter of inner conviction, as for a judge or a jury" (Auriche & Loupi, 1993). Agreement among the experts, that is to say the judge or jury's inner convictions, on the probability of a causal relationship could be less than 50 percent (Naranjo et al., 1992).

One study also reported wide disparities between the clinical pharmacologists' judgment and those of the physicians reporting 500 suspected adverse drug reactions (Koch-Weser, Sellers, & Zacest, 1977). Not only did the pharmacologists disagree with the physician assessment but the three expert pharmacologist reviewers disagreed among themselves 36.4 percent of the time on the drug most likely to have been responsible for the adverse drug reaction, 56.8 percent of the time about whether the adverse drug reaction caused a hospital admission, 55.8 percent of the time about the severity of the morbidity from the adverse drug reaction, 67.3 percent of the time on whether the adverse drug reaction prolonged hospitalization, and 71 percent of the time on whether the adverse drug reaction contributed to death.

A similar study reported that the clinical pharmacologist experts reviewing 60 selected cases completely agreed with the treating physicians in 47 percent of the cases (Karch et al., 1976). They had complete agreement among each other in 50 percent of the cases.

Because of this lack of agreement among experts, several researchers developed algorithms in an attempt to enhance agreement between raters. By standardizing the most useful factors to be considered when assessing a causal relationship, the researchers hoped to gain both reviewer consensus and some idea of what the "truth" was. The

algorithm developers incorporated some version of the factors that the Food and Drug Administration (FDA) uses today. These factors included a temporal relationship between the agent and reaction, dechallenge, rechallenge, other etiologies, previously known toxicities, and lab tests (Food and Drug Administration, 2001).

Even though there were many algorithms developed, there were three that were the most widely cited and used (Jones, 1982; Kramer, Leventhal, Hutchinson, & Feinstein, 1979; Naranjo et al., 1981). These causality assessment methods shared a common basic structure. First, they posed questions regarding the specific case of suspected adverse drug reaction. These questions pertained to the timing and clinical characteristics of the case in order to assess whether they were consistent with an adverse drug reaction. Next, the answers were converted into a probability that the adverse reaction was caused by any of the drugs to which the patient was exposed (Hutchinson & Lane, 1989).

The algorithm by Jones was the algorithm used at that time by the FDA's Division of Drug Experience. It concentrated on four elements of adverse drug reactions: temporal relationship, dechallenge, rechallenge, and alternative etiologies. The responses were categorized as remote, possible, probable, or highly probable (Jones, 1982). Unlike Naranjo and Kramer, Jones did not assign a numbered weighting system to delineate categories. Although easy to use, it lacked some depth in its interrogation.

A simpler, more widely used algorithm was the 10-question format developed by Naranjo and colleagues (Table 4) (Naranjo et al., 1981). Scores ≥ 9 were labeled

definite, scores from 5 to 8 were labeled probable, scores from 1 to 4 were labeled possible, and scores of ≤ 0 were labeled doubtful.

Table 4. Adverse drug reaction probability scale (Naranjo et al., 1981)

	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score				

The third algorithm involved a more complex and detailed flowchart (Hutchinson et al., 1979; Kramer et al., 1979). This algorithm was scored on six axes: 1) previous experience, 2) no alternative illness, 3) timing of events, 4) drug levels, 5) dechallenge, and 6) rechallenge. A collapsed version of the flowchart diagram also offered a useful understanding of Kramer's approach (Mannesse et al., 2000).

With a possible scoring range of +7 to -7, the summed scores were classified as definite (score + 6 to +7), probable (score +4 to +5), possible (score 0 to +3), or unlikely (score less than 0). While this algorithm addressed most of the criteria an expert would use when assessing causality, its unwieldy and lengthy, 56-question format was one of the driving forces behind Naranjo's efforts to develop a simpler mechanism.

A study comparing these three algorithms found that the Naranjo and Kramer algorithms compared favorably to each other (67 percent agreement, 0.43 weighted

kappa) as did Jones and Kramer (67 percent agreement, 0.48 weighted kappa) (Michel & Knodel, 1986). The agreement between Jones and Naranjo was 64 percent but the weighted kappa was only 0.28. This study considered Kramer's algorithm the gold standard. The small sample size of 28 adverse drug reactions limited any conclusions about which algorithm preformed best. The study design did not allow them to demonstrate whether the algorithms performed any better than expert opinion would have.

A study that compared the assessments of 40 adverse drug reactions between four algorithms and 14 expert reviewers showed poorer levels of agreement between the algorithmic methods of causality (weighted kappa 0.40) compared to expert opinion (weighted kappa 0.55). The authors of this study suggested that the structured methods offered little advantage over the traditional judgmental methods; yet, the sample size limited this conclusion (Lee, Rawlins, & Smith, 1992).

Stephens cited at least 17 papers comparing, criticizing, or commenting on 18 different adverse drug reaction algorithms (Stephens, 1987). Girard strongly criticized algorithms as merely a means to reconcile experts rather than to precisely describe adverse drug effects (Girard, 1984). Girard argued that algorithms implied an absurd assumption that a consensus of experts was not reliable. He insisted that the experts were being forced to relinquish their competence as experts by allowing the final responsibility for determining causality to an algorithm; an algorithm that was subjectively developed since very few authors proved how the objective criteria were derived nor how the weighting systems of their algorithms were assigned.

Another commentary severely critical of the structured assessment measures maintained that the probability of drug causation is a subjective measure of the reviewer's uncertainty and that the structured methods do not perform the job for which they were designed (Hutchinson & Lane, 1989). They contended that this method was flawed because, to avoid disagreements between evaluators, the questions were posed in a dichotomous yes or no fashion. None of the questions assessed to what degree the reviewer believed in the response. This potentially forced a false consensus.

While the debate over algorithm versus expert opinion in assessing causality continued, several other issues were often overlooked. Would the reaction have occurred no matter what drug the patient took? Previous research showed that merely administering a placebo could result in the patient experiencing adverse effects: some severe enough to result in discontinuation of the placebo (Green, 1964). The literature also suggested that it was important to determine a pretreatment incidence of symptoms or a background rate; yet, this was rarely assessed in the studies of adverse drug reactions (Green, 1964; Jick, 1974). The risk in unexposed patients is never null (Begaud, Moride, Tubert-Bitter, Chaslerie, & Haramburu, 1994). A survey of 414 subjects without illness and taking no medications for at least three days, found that only 19 percent of subjects had none of the 25 side-effect symptoms listed (Reidenberg & Lowenthal, 1968). This meant that 81 percent of these healthy subjects experienced at least one of the most common symptoms of an adverse drug reaction without receiving a drug.

A plethora of other mitigating factors also clouded the interpretation of a causal effect (Gordon, 1985). Concomitant drugs, other pathologies, and inappropriate drug use

are just of few factors that must be considered when trying to establish blame for a reaction on a particular agent. Biological plausibility must be considered as well (Rawlins, 1995). Researchers who attempted to use the algorithms in a study on drug-related deaths found the algorithms problematic because in order to achieve a higher probability score a dechallenge or rechallenge was needed (Ebbesen et al., 2001; Liu, Knowles, Mittmann, Einarson, & Shear, 2001). Of course this was impossible to do on a dead patient. The algorithms also failed to add points for postmortem drug analyses' or autopsy findings (Ebbesen et al., 2001).

Along with the previously mentioned factors, consideration must also be given to the methods used for adverse drug reaction data collection and identification. Not only does the data collection method influence the reported incidence rates but some methods infer a greater confidence in the causal link than others (Bennett & Lipman, 1977).

Adverse drug reaction data identification methods

Along with the ability to support or dispel suspicion of a causal relationship, the method of adverse drug reaction identification affects the ability to calculate adverse drug reaction incidence rates. In order to calculate an adverse drug reaction incidence rate, the number of patients-at-risk is needed. The number of patients exposed to a drug is rarely known so researchers resort to using proxies of patient exposure. The more common proxies include prescription audits, sales data, or physician and patient surveys (Gordon, 1985). Because the patient-at-risk denominator is unknown, adverse drug reaction studies are often misleading by reporting results as incidence rates when they are actually reporting frequencies. Still, the term incidence abounds in the adverse drug reaction

literature despite the fact that few studies actually measured incidence (Waller, 1992). Waller suggested that the most suitable analytic method for measuring the incidence of an adverse drug reaction may be through life tables, since this method accounts for both the differential duration of exposure and a non-constant time function; yet, this method was little used (Abt, Cockburn, Guelich, & Krupp, 1989). The adverse drug reaction studies in the literature used a number of different approaches to collect adverse drug reaction data.

Spontaneous voluntary and solicited reporting

Spontaneous or voluntary reporting of adverse drug reactions was the backbone of adverse drug reaction reporting in the post-approval stage for decades (Fletcher, 1991; Venulet & Ten Ham, 1996). This method depended on the willing participation of the health care professional to file a report of the reaction with either a regulatory agency or within their organizational hierarchy. The U.S. Food and Drug Administration has maintained an adverse drug reaction reporting program since 1960 (Jones, 1982). Theoretically, a surveillance system based on spontaneous reporting is conducted on all patients within the treated population and is not restricted to an *a priori* hypothesis (Begaud et al., 1994). This results in an opportunity for a large-scale review and a relatively inexpensive method of detecting rare, serious, adverse reactions that were not uncovered during smaller clinical trials (Venulet & Ten Ham, 1996).

Spontaneous reporting has several important limitations that affect the ability to assess causality. First, if the previously known toxicity of the drug is considered in the stream of causality assessment factors, then the underreporting of adverse drug reactions

that plagues the spontaneous reporting system reduces the ability to assess causality and the ability to establish true incidence rates of adverse drug reactions. At issue is the fact that the number of reports needed to establish that Drug A caused Reaction B is unknown and dependent upon the quality of the report. Consideration must be given to the fact that Reaction B was instead caused by an underlying disease rather than Drug A. A monitoring system based on spontaneous reporting cannot capture adverse effects that manifest themselves as a highly prevalent disease (Moore, Psaty, & Furberg, 1998).

Just one or two well-documented individual reports could be the major stimulus for labeling or regulatory changes (Jones, 1982). It is rare, however, that the spontaneous adverse drug reaction report is actually confirmed (Sachs & Bortnichak, 1986). Often the reports lacked information such as co-morbidity or concurrent medication information that was essential to discerning causality (Venulet & Ten Ham, 1996). Therefore, while the spontaneous reporting system was designed to serve well as a signal to stimulate research on the rare, bizarre event, it did poorly in measuring the more common events, and thereby became useful only for raising hypotheses of possible adverse drug effects (Begaud et al., 1994; Jones, 1982; Sachs & Bortnichak, 1986; Strom & Tugwell, 1990).

The extent of underreporting is unknown. Underreporting may be as high as 98 percent, with some data indicating that a single spontaneous report may imply the existence of 50 more similar events in the total exposed patient population (Fletcher, 1991). Between 85 percent and 98 percent of physicians, depending on the country, never reported adverse drug reactions to a national authority (Fletcher, 1991; Venulet & Ten Ham, 1996). Reports on Britain's yellow card scheme, estimated that it was rare for

more than 10 percent of serious reactions to be reported and that reporting for non-serious reactions was even worse at 2 percent to 4 percent (Rawlins, 1995). The poor reporting by hospital physicians was cited as part of the problem. Only a third of reports came from hospital physicians despite the fact that the majority of serious reactions occur in hospitals. In a 1988 survey only 57 percent of 1211 surveyed physicians were aware of the FDA's reporting system and only 21 physicians (1.7 percent) reported adverse drug events to the FDA (Smith Rogers et al., 1988).

In conjunction with the underreporting is the inability to assess if reported cases differ from non-reported cases in terms of severity, time to onset, risk factors, and various other characteristics (Begaud et al., 1994). Report bias is a limitation of spontaneous reporting systems. Spontaneous adverse drug reaction reports were shown to be affected by the length of time the drug was on the market. Reports peaked at the end of the second year of marketing and declined after that despite no decline in usage nor evidence that the actual incidence of adverse reactions had changed (Sachs & Bortnichak, 1986).

A study that examined the adverse drug reaction frequencies among eight drugs that had been removed from the market and 14 randomly selected drugs concluded that drugs with more safety concerns had higher adverse drug reaction frequency rates within the first 2 years of marketing as compared to drugs with fewer safety concerns (Ajayi, Sun, & Perry, 2000). Drugs with fewer safety concerns tended to have rates that reached a plateau after approximately 2 to 3 years of marketing and maintained a consistent frequency of adverse drug reactions over time. Four of the drugs in their sample were

removed from the market in under two years. The remaining four drugs showed a distinct drop in their adverse reaction frequency curves after year two.

Another potential bias needing consideration was if and how foreign and domestic data were merged. Because drugs are approved for different indications and prescribed in different usage patterns in different countries, the population-at-risk can differ between countries and alter the adverse drug reaction potential (Sachs & Bortnichak, 1986). Indiscriminate merging of data from these different sources could lead to an inaccurate conclusion.

A second issue that could lead to biased conclusions when considering foreign and domestic adverse reaction reports was the differences in reporting requirements between countries (Sachs & Bortnichak, 1986). The reasons, mechanisms, and rates of reporting to the various regulatory agencies varied by country and could result in wide disparities in reporting rates. A look into national differences in spontaneous adverse drug reactions reporting rates for piroxicam illustrated this. For every one report in the United States, the United Kingdom had twice the number of reports, Sweden 3.3 times as many reports, and Germany only one third as many.

The adverse drug reaction environment was a third bias issue. An increase in spontaneous reporting may have occurred merely because of a temporal effect bias (Sachs & Bortnichak, 1986). Adverse drug reaction reporting peaks with positive or negative reports published in major journals (Edlavitch, 1988). External factors such as a change in reporting system or level of publicity can alter the reporting rates (Sachs & Bortnichak, 1986). For example, the removal of cerivistatin from the market in August,

2001 because of the increased frequency of rhabdomyolysis was well publicized. Obviously, patients and physicians would start looking for the signs and symptoms of this problem when any of the other remaining drugs in this class were used. An adverse drug reaction researcher detecting a higher rate of spontaneous reporting of this reaction connected with this class of drugs needs to take this into consideration when deciding whether this was a true increase in incidence versus an increase in reporting due to consumer alertness.

Besides the bias and underreporting problems, perhaps the most important limitation of spontaneous adverse drug reaction reporting is the lack of accurate numerator and denominator data. Unlike clinical trials, in the post-marketing environment, the user population and drug exposure patterns are rarely known. Without a known population-at-risk (denominator) and only an unknown fraction of adverse drug reactions (numerator) getting reported, any calculated incidence rate is at best an estimate and at worst completely baseless (Food and Drug Administration, 2001; Koch-Weser, 1968; Strom & Carson, 1990; Strom & Tugwell, 1990). Without an adequate denominator, the true measure of risk cannot be calculated (Friedman, Collen, Harris, Van Brunt, & deBoer, 1971). Yet, even without denominator data, spontaneous reporting may be of some help in identifying risk factors when the characteristics of affected individuals can be described (Waller, 1994).

Chart review

Most of the studies on adverse drug reactions entailed medical record or chart review at some point in the process, either retrospectively or prospectively. When

performed prospectively this method was sometimes called intensive surveillance. When performed retrospectively, it was often done through discharge review of patient charts. The chart review process was used in some studies as an identification mechanism for adverse drug reactions or, in others, as a confirmation mechanism. Researchers prospectively reviewed each of the targeted patient's medical records searching for physician documentation of unreported adverse drug reactions. Some researchers developed a list of target indicators that would flag those records that were highly suspected of having an adverse drug reaction. Only the flagged records would be reviewed.

No matter the mechanism taken, medical record review was severely limited by the lack of physician documentation of adverse drug reactions and the poor quality of the documentation. Lack of documentation could be due to lack of physician suspicion or recognition of an adverse drug reaction as well as a myriad of other reasons (Leape, 1999; Schumock et al., 1991). The failure to document an adverse drug reaction in the medical record affected the numbers of adverse reaction reports and contributed to underreporting of adverse drug reactions; whereas, the poor quality of the documentation affected the ability to assess a causal association between a specific drug and the reaction. In addition, the adverse drug reaction definition the researchers used during medical record review affected the frequency of the adverse drug reactions found through this method as well as the ability to compare the conclusions of various studies.

The strength of medical record review was that when an adverse drug reaction was found, there was a greater possibility of confirming a causal effect (Venulet & Ten

Ham, 1996). Since the numerator (number of adverse drug reactions) was known, the frequency of events in the specified population could be calculated. Logistical and privacy act issues tended to restrict this method to hospitalized patients.

Spontaneous reporting and record review are easily the two most frequently used methods of adverse drug reaction detection. Although not limited specifically to adverse drug reactions, a study by O'Neil compared the two methods in their ability to identify adverse medical events. She found that the housestaff physician reported nearly the same number of adverse events as record review, 89 versus 85, respectively, but only 41 of the same patients were identified by both methods (kappa 0.52) (O'Neil et al., 1993).

The trade-off for an ability to confirm the adverse drug reaction with record review came at the price of a very labor-intensive process. The cost of the physician reporting mechanism in O'Neil's study was $15,000 compared with $54,000 for record review. Because few facilities have the luxury of the personnel or the funds to devote to routine medical record review for adverse drug reactions, other detection mechanisms combining several different screening methods were pursued.

Diagnostic coding

Certain event codes (E-codes), as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) system, are specific for adverse drug reactions. Researchers identified potential adverse drug reactions with the E-code and then reviewed the medical record to validate proper coding and to verify a causal relationship (Schumock et al., 1991). Coding occurs after discharge so the results are more accurately referred to as hospital separations rather than hospital admissions

data (Roughead, 1999). Coders assigned the E-codes based upon physician documentation in the medical record; therefore, this method still suffered from the lack of documentation issues that plagued the chart review method.

A two year Australian study used E-codes to assess the reporting of adverse events in inpatients (O'Hara & Carson, 1997). They found that 19 percent of the separations with adverse event codes were due to adverse drug effects (codes E930-E949: drugs, medicinal and biological substances causing adverse effects in therapeutic use). Systemic agents (14.9 percent), cardiovascular agents (14.2 percent), antibiotics (13.1 percent), analgesics and antipyretics (11.3 percent), agents affecting blood constituents (7.4 percent), hormones and synthetic substitutes (7.2 percent), and psychotropic agents (7.1 percent) were the most frequently coded adverse drug effects.

The accuracy of the coding has been debated but Roughead's study countered that the coding was in fact accurate, but only 11-31 percent of all adverse drug reactions were reported (Roughead, 1999). Thus, lack of documentation or underreporting appeared to be a bigger limitation than miscoding. Since ICD-9-CM coding was dependent upon written documentation by prescribers, the suspicion that the drug caused the reaction was theoretically stronger than it was with some of the other screening methods. More extensive use of the E-codes has been encouraged through the addition of a labeled space on the coding form and through changes in state reporting requirements (Centers for Disease Control and Prevention, 1994; Centers for Disease Control and Prevention, 1997).

Screening of laboratory tests

Laboratory values of serum drug concentrations that were at high or toxic levels were used as adjunct detection methods in some studies. This method was limited to drugs in which drug serum concentrations were feasible or where the drug's effects altered measurable organ function parameters, as well as, to drugs in which serum concentrations could be correlated to adverse drug reactions. Laboratory tests were excellent tools for establishing a causal link to an adverse event but still required medical record review or patient interview in order to confirm an adverse drug reaction because a high drug concentration on its own does not mandate that the patient suffered any adverse reaction. Yet, rather than having to review the charts of the entire patient population, the researchers could limit the chart review to the records that were flagged by the lab report screening. This made the reviewing task less labor-intensive.

A two month Israeli study tested the potential of automatic laboratory signals to alert for adverse drug reactions (Azaz-Livshits et al., 1998). This study compared the sensitivity of an automatic lab signal (ALS) method against the gold standard chart review. The study defined an adverse drug reaction as an event that prolonged hospitalization or caused discomfort. The lab values consisted of three measures of hematological functioning, five measures of liver functioning, two measures specific for renal functioning, two measures for electrolyte disturbances, one for metabolic disturbances, and seven drug-specific therapeutic plasma levels.

Forty adverse drug reactions were detected by chart review in 38 of 153 admissions. The ALS system identified 26 out of 40 adverse drug reactions identified by

chart review (65 percent). The sensitivity of the ALS method was 65.8 percent (25 of 38 adverse drug reaction admissions). ALSs were generated in 56 of 115 adverse drug reaction-negative admissions yielding a specificity of 51.3 percent.

Bates estimated that the use of abnormal lab results as a screening technique could potentially detect 29 percent of adverse reactions (Bates et al., 1994). This, along with Azaz-Livshits' conclusions suggests that lab screening is a supplement to other detection methods.

Screening of medication orders

It is well known that certain medication orders stimulated suspicion that an adverse drug reaction occurred. Orders for dose reductions, for antidotes such as protamine or vitamin K, for symptom relief medications such as diphenhydramine, or for discontinuation of a drug were indicators that raised flags that an adverse drug reaction may have occurred and that further review was required. Just as with the lab screening, medication order screening could not establish that an adverse drug reaction occurred without verification by chart review; yet, it was a good method of focusing the researcher's attention onto the patients' records with the strongest suspicion of an adverse drug reaction.

A small but interesting study by Berry compared the sensitivity and specificity of three methods of detecting adverse drug reactions: screening of lab reports, pharmacist screening of medication orders, and voluntary reporting (Berry, Segal, Sherrin, & Fudge, 1988). Chart review served as the reference method. The study targeted patients on any of three drugs: digoxin, theophylline, and gentamicin. The 98 patients selected could be

on one, two, or all three. Eleven patients with adverse drug reactions were detected by the reference method. Laboratory reports flagged 49 charts, pharmacist screening 22 charts, and voluntary reporting flagged none.

Sensitivity was calculated as the percentage of charts including adverse drug reactions (as identified by chart review) that the detection method flagged as positive. The lab screening method detected all eleven charts (sensitivity of 100 percent), pharmacist screening detected six (sensitivity of 54.5 percent), and the voluntary reporting detected zero (sensitivity 0 percent).

Specificity was calculated as the percentage of charts that did not include adverse drug reactions as detected by chart review that the detection method identified as negative or did not flag. The lab screening method detected 38 charts (specificity 56.3 percent), pharmacist screening detected 16 (specificity 81.6 percent), and voluntary reporting 0 (specificity 100 percent).

Although the small sample size of this study limited the conclusions that could be drawn from it, the study showed that automated detection methods held promise, especially when used in combination with each other. Computerized surveillance has become an increasingly useful and used method (Azaz-Livshits et al., 1998; Classen et al., 1991).

Integrated computerized surveillance

Advances in computerized medical records opened up new methods for detecting adverse drug reactions. Computerized surveillance integrated the signals used in the laboratory and pharmacy order screening methods with computerized medical records

information. The beauty of this method was the ability to integrate the signals between the databases and create a hierarchy of events that provided additional support for causality assessment. Although laboratory, pharmacy, and radiology data are highly computerized, very few organizations actually computerized the entire patient medical record; therefore, the suspected adverse drug reactions identified by the integrated screening still had to be manually assessed for causality. Thus, record review, physician or nurse contact, or patient interview was still required to confirm and assess an adverse drug reaction.

Along with manual review, the thoroughness of the computer program used to identify an adverse drug reaction was important in order to avoid identifying events that were not reactions (false positives), as well as to avoid failing to identify reactions that did occur (false negatives), and was a major issue in the use of computerized surveillance; however, the computerized program was only as good as the program writers. A movement toward a fully computerized patient record highlighted even further the problems faced by the computer program architects.

Gabrieli discussed at length the issues and perils surrounding the use of computerized medical records for adverse drug reaction study (Gabrieli, Gabrieli, & Rosen, 1985). In circumstances where a medical record was completely computerized, vocabulary was unrestricted. Natural language expressed the same meaning in a myriad of ways. For example, when a patient complained of dizziness, the records contained 14 variations of the theme: stunned, mentally confused, dazed, whirling sensation, tendency

to fall, weakness, giddiness, vertiginous, head swimming, faintness, drawn into a whirl, light-headedness, unsteadiness in thought, and queer in the head.

Another complicated step in computerized surveillance was to separate the clinical manifestations into either a disease manifestation or an adverse drug reaction. These causes were not mutually exclusive. Because they are not, the task becomes more difficult since the reality is that the clinical manifestations may belong to both classes, so rather than handling the decision as a binary yes/no outcome, a probability assessment had to be made. The computer programmer is forced into creating multiple algorithms.

A voluntary reporting system was compared with the screening done through computerized medical records (Classen et al., 1991). The computerized record contained integrated patient information drawn from pharmacy, laboratory, surgery, and radiology sources. Computer programs were written that targeted various signals for an adverse drug reaction. The adverse drug reactions identified in this report were then investigated by a combination of chart review, physician or nurse contact, or patient interview to determine causality. Assessment of the probability of an adverse drug reaction was made using the Naranjo algorithm. Of 731 adverse drug reactions recorded, 641 (87.7 percent) were detected through the automated method.

The signals that were programmed to detect potential adverse drug reactions included discontinuation of medications, decreases in dosages, ordering of known antidotes, ordering of specific lab tests such as *Clostridium difficile* toxin assays, and specific lab test abnormalities. The most common signals of the confirmed adverse drug

reactions were generated by antidote use (41.3 percent), therapeutic drugs for adverse drug reactions (16.9 percent), and drug levels (16.5 percent) (Classen et al., 1991).

The major antidotes that generated signals were diphenhydramine hydrochloride (32.7 percent) and naloxone hydrochloride (8.6 percent). Phytonadione (7 percent), antidiarrheals (6.7 percent), and sodium polystyrene sulfonate (1.2 percent) were the most common therapeutic agents used to treat adverse drug reactions. Epinephrine signaled one adverse drug reaction.

While Classen's study was able to increase their detection and reporting frequency by 60-fold, they did not disclose their number, if any, of false positives produced by the automated system. This becomes an important element when attempting to eliminate the time-consuming medical record review portion in favor of a completely automated detection system.

The methods discussed thus far are dependent upon a fairly short time lag between drug administration and the adverse reaction. The Annual Adverse Drug Experience Report: 1996, stated that about half (52.8 percent) of the 85,517 cases reported with a drug administration date occurring before the adverse experience date noted the adverse event occurred within one week of drug initiation, 6.1 percent occurred between 8 and 14 days, and 7.5 percent occurred between 15 and 30 days for a total of 66.4 percent of the cases occurring in 30 days or less from drug initiation (Food and Drug Administration, 2001). Slightly more than 10 percent of the reactions occurred greater than 365 days after drug initiation. Ninety-three percent of post-discharge adverse drug reactions occurred within 14 days of discharge (Letrilliart et al., 2001). Similarly, the

onset of fatal adverse drug events occurred ≤ 31 days after drug initiation in 67.4 percent of the cases while 25 percent occurred during the first 24 hours and 10.3 percent occurred after 365 days (Kelly, 2001a). A longer interval between drug dosing and adverse reaction lowers the chances that a causal connection will be discovered (Venulet & Ten Ham, 1996).

Monitoring population health changes

Changes in the population morbidity and mortality statistics could be a source for detection of adverse drug reactions with longer latency periods. Monitoring the population surveillance registers was beneficial in identifying an increase in mortality in young asthma patients and establishing the causal role of a drug that had only been assumed up until then (Venulet & Ten Ham, 1996). These registers are made up of national health statistics information and data received from special registries. This method was little used in adverse drug reaction detection. Exposure status was rarely available from these registers so findings were hard to interpret thereby limiting the usefulness to hypothesis generation.

In the United States, the primary sources of population data on mortality from adverse drug reactions are from death certificates and FDA reports (Chyka, 2000). The National Center for Health Statistics compiles data on cause of death, both primary and contributory, from the death certificates filed in all 50 states and the District of Columbia. The FDA reports on adverse drug reactions are captured through the spontaneous post-marketing surveillance program, MedWatch. Using 1995 data Chyka compared these two sources and found a 34-fold difference between them. Only 206 out of 2.3 million

deaths were attributed to adverse drug reactions in the death certificate group but 6,894 deaths were reported in the MedWatch group.

Estimates of adverse drug reaction and/or event deaths have been extrapolated based on individual study results yielding a range of 200 to 200,000 deaths per year (Brennan et al., 1991; Lazarou, Pomeranz, & Corey, 1998). Chyka found values up to 100-fold less than the values estimated by these extrapolations and emphasized the danger in extrapolating the results from a study-specific surveillance program into a national rate (Chyka, 2000). The surveillance programs may have included sicker patients, occurred in high-risk settings, or been subject to sampling bias.

On the opposite end of the population-based mode of identification is the individual self-reporting method.

Patient self-reporting

Physicians generally ask their patients how they tolerated a drug and make therapeutic decisions based upon patient responses. Unfortunately, physicians do not often document that an adverse reaction was the reason for a therapeutic change or whether the reaction resolved with the medication change.

Patient interviews could potentially uncover interactions that went undocumented in the medical record. Recall bias was a concern with this method. Discerning a temporal relationship between drug and reaction was difficult with this method unless the patient could accurately recall when symptoms began and confirming drug exposure was found within a pharmacy database or medical record. An assumption that drug prescription equals drug consumption was also a potential weakness of this type of study.

A study comparing patient surveys with retrospective chart reviews was conducted in 11 Boston-area ambulatory clinics. The study compared the frequency of drug complications reported by patients in a telephone interview versus that found in the patient's chart (Gandhi et al., 2000). Those patients who were surveyed also had their medical records reviewed for physician-documented adverse drug events using the Naranjo algorithm to classify the events.

Among 2,248 patients taking prescription drugs, the patient survey method found 394 drug complications (17.5 percent) compared to 64 adverse drug events discovered during chart review (2.8 percent). Only 26 (6 percent) were identified by both methods. Although events detected by both methods did not differ in severity, patients whose events were detected by both methods were more likely to seek medical attention than those whose events were detected by survey alone ($p = 0.03$).

The disparity between what the patient reported versus what was documented in the chart could have been caused by patient failure to report a problem to their physician and the physician's failure to document a problem or, since there was no method to assess causality in the survey arm of the study, the complication may not have been drug related at all. The authors suggested an integration of adverse event detection methods, for example self report and record review, since different collection methods captured events that were not captured by other methods.

In contrast to Gandhi's disparity between patient report and chart documentation, an older study found that after a review of patient records, 78 percent of the patient reports of an adverse reaction were authentic (Meleney & Fraser, 1969).

No matter the collection method, merely reporting the numbers of adverse drug reactions that occurred aids little in the search for ways to prevent the adverse reactions. Identification of patient risk factors for adverse drug reactions is essential for developing prevention tactics.

Adverse drug reaction risk factors

Risk factors for adverse drug reactions evaluated in the literature include age, sex, number of prescribers, number of pharmacies, number of concomitant medications, and number of co-morbid conditions. These risk factors will be discussed in this section.

Age as a risk factor for adverse drug reactions

The pharmacodynamic and pharmacokinetic differences unique to the very young and to elderly patients potentially predispose them to adverse drug reactions (Ajayi et al., 2000). It would seem that neonates in neonatal intensive care units (NICU) would be at particular risk of adverse drug reactions for several reasons. Neonates in the NICU are usually more critically ill, receiving multiple drugs, and have incompletely developed organ systems that may dramatically alter the response to drugs (Knight, 1994). Study of adverse drug reactions in this population was far less extensive than in the adult population. One group found that among 3,026 NICU admissions, only 0.2 percent were due to adverse drug reactions (Mitchell et al., 1988). In addition, they found that among 6,546 children admitted to one of five hospitals, 2 percent of the admissions were due to adverse drug reactions.

A surveillance program of pediatric outpatients recorded adverse symptoms in 473 (11.1 percent) of 4,244 separate courses of drug therapy (Kramer et al., 1985). This study found a slightly increased risk (RR = 1.35, 95% CI = 1.01-1.80) of an adverse drug reaction in children less than 12 months relative to that in older children, but an inpatient study of adverse drug reactions in children from 1 month to 24 months old did not find a particular age predisposition (Martinez-Mir et al., 1999). Kramer's study, along with Mitchell's work, appeared to concur that adverse drug reactions occur less frequently among neonates and children and are much milder and self-limiting than in the adult population (Kramer et al., 1985; Mitchell et al., 1988).

A meta-analysis found the overall incidence of adverse drug reactions in hospitalized children was 9.53 percent (95% CI = 6.81-12.26) (Impicciatore et al., 2001). Pediatric hospital admissions secondary to adverse drug reactions was 2.09 percent (95% CI = 1.02-3.77). Outpatient children had an overall incidence of adverse drug reactions of 1.46 percent (95% CI = 0.7-3.03). Among the 17 studies included in the meta-analysis, only one included information on different age groups; therefore, it was not possible to address changes in adverse drug reaction frequency with advancing age (Menniti-Ippolito et al., 2000). The inclusion criteria for this meta-analysis required that the population not be selected for particular conditions nor drug exposure and use prospective monitoring to identify adverse drug reactions (Impicciatore et al., 2001). The researchers did not discuss whether there were any restrictions on the definition of adverse drug reaction used in the study. An inconsistency of definitions between studies could have influenced the results.

While there was limited study of adverse drug reaction risk in children, there was more abundant study in adults. A large study done in Medicaid patients reported an association between age and risk of hospitalization (Saltsman & Hamilton, 1999). In this study 55,744 matched pairs of Medicaid cases (hospitalized patients) and controls (non-hospitalized patients) were used to identify how age, sex, the number of prescribers, the number of pharmacies, and the number of medications affected the risk of hospitalization in general. Each variable alone significantly affected the risk of hospitalization but when using multivariate logistic-regression, they found that only age, sex, number of prescribers, and the number of medications were statistically significantly different between cases and controls. In addition, interaction terms between age and number of medications, sex and number of medications, and number of prescribers and sex were found to significantly improve the fit of the final model. If these factors predicted who was admitted to the hospital, then one would expect to see age recognized as a risk factor in the studies on adverse drug reactions, but this was not found consistently among the studies.

An association between increasing age and adverse drug reactions was frequently mentioned but few researchers assessed whether the frequency was attributable to age alone. The fact that the number of coexisting illnesses increased with age, as did the number of medications prescribed, was rarely addressed. Evaluation of spontaneous adverse drug reaction reports, known as yellow cards, sent to the Committee on Safety of Medicines in Southhampton from June 1964, through April 1985, showed that the proportion of reports received for the elderly increased over that time from 24 percent of

the total yellow cards in 1965 to 35 percent in 1983, while the elderly proportion in the population rose by only 1 percent during that time (Castleden & Pickles, 1988). Concurrent with this increased proportion of reports on the elderly was a corresponding correlation between the use of drugs in this population and the number of adverse drug reaction reports.

Logically, an increased exposure should mean an increased opportunity to experience an adverse drug reaction. The unavailability of this exposure information was evident in the studies of adverse drug reactions in hospital admissions because the number of patients in the relevant community exposed to drug treatment should be the true denominator for these studies, not the total number of patients admitted to the hospital (Nolan & O'Malley, 1988). Again, since increasing age has an association with hospitalization, one would expect to see a greater proportion of elderly patients admitted due to adverse drug reactions.

None of the studies that found an association between age and adverse drug reactions evaluated the association after controlling for the effects of sex, number of medications, or number of prescribers. Four of the studies that failed to find an association between age and adverse drug reactions controlled for at least one other variable. The most notable of these was a large multi-center trial from Italy (Carbonin et al., 1991).

Of the 9,148 patients admitted during two observation periods of two months, there were 532 (5.8 percent) probable or definite adverse drug reactions as determined by the Naranjo algorithm and using the WHO definition of adverse drug reactions. In a

univariate analysis, frequency of adverse drug reactions increased from 3.3 percent in patients under 50 to 6.4 percent in ages 50-59, 6.2 percent in ages 60-69, 6.5 percent in ages 70-79, and 5.8 percent in ages 80 and over ($p < 0.0001$). In the multivariate logistic model, however, age fell out of the model and was no longer a significant independent predictor of adverse drug reactions. Instead, the number of drug prescriptions, hospital stay duration, and number of active medical problems were the strongest predictors of an adverse drug reaction with odd ratios of 2.94 (95% CI = 2.38-3.62), 2.82 (95% CI = 2.26-3.52), and 1.78 (95% CI = 1.29-2.45), respectively. Likewise, in a study of drug-drug interactions, age was related to the incidence of potential interactions in the simple regression analysis but was not when a multivariate regression analysis was done using age, number of prescribed drugs, hospital stay, and diagnosis as independent variables (Kohler et al., 2000).

When adverse drug reaction studies reported an association between age and adverse drug reactions, they generally reported an increase in adverse drug reactions with an increase in age. An Iowa survey of 3,170 community-dwelling persons 65 years and older was one of the few studies to find a decreasing adverse drug reaction frequency with increasing age (Chrischilles et al., 1992). This trend was only significant in women ($p = 0.003$; men, $p = 0.10$) but the negative association persisted in the multivariate model after controlling for poorer health status and more medication use. The authors postulated several reasons for the negative trend, including the limitation of their study population to those 65 years or older. Previous studies reported on much wider age ranges. This trend could also represent a survival effect, meaning that ambulatory older

people were generally healthier, thereby requiring fewer medications because they suffered from fewer health problems. It was also possible physicians modified their prescribing in the oldest patients to avoid adverse drug reactions.

Another possibility was that the negative association could have been due to differences in reporting and detection of adverse drug reactions between younger and older segments. This study used a self-reporting survey design. Patient recall and assignment of a problem to their drug therapy might have differed between the groups. It was speculated that a diminishing frequency in the very old might not be real but a consequence of the difficulty in detecting mild adverse drug reactions in this segment of the population (Carbonin et al., 1991).

While there appears to be a relationship between advancing age and adverse drug reactions, the interaction between age and the co-morbidities and polypharmacy that can be experienced in tandem with the aging process must be considered.

Gender as a risk factor for adverse drug reactions

Similar to age, the reported association between sex and adverse drug reactions did not bear out consistently across studies. Several studies reported a difference in adverse drug reaction frequencies between males and females. Although some studies found no difference in adverse drug reactions between the sexes, those that did found a propensity for females to experience more reactions (Martinez-Mir et al., 1999; Tran, Knowles, Liu, & Shear, 1998). Reasons postulated for this difference included a variation in drug exposure (polypharmacy), differences in drug pharmacokinetic and pharmacodynamic properties, differences in event perception, and treatment of gender-

specific conditions (Drici & Clement, 2001; Harris, Benet, & Schwartz, 1995; Rademaker, 2001).

Naturally, if one sex receives more exposure to medications than another, then they would have a greater opportunity to experience an adverse reaction but the purported gender difference in the acquisition of prescription medication was debated (Svarstad, Cleary, Mechanic, & Robers, 1987). Svarstad argued that the gender differences were virtually eliminated after accounting for female-specific diagnoses and the drug categories used exclusively to treat female-specific conditions.

Only one of the studies that reported a higher frequency of adverse drug reactions in females actually controlled for confounding factors (Gray et al., 1999). This study reported on 256 patients aged $\geq$ 65 years who received home nursing after hospital discharge and completed a one-month post-discharge interview. Variables that were entered into multivariate logistic models were those that reached a significance level of $p < 0.15$ in the univariate model. These variables were sex, Mini-Mental State Examination (MMSE) score, and number of new scheduled medications at discharge. The multivariate analysis found that females were 2.26 times as likely as males to have an adverse drug reaction in this population (95% CI = 1.06-4.77).

Gray's study was one of the few that applied relevant interaction terms to the model. An assessment of interaction terms was not reported in Carbonin's study. Carbonin's study found that neither age nor sex were independent risk factors for an adverse drug reaction. The strongest predictor of adverse drug reactions in this study was the number of drug prescriptions (OR = 2.94) (Carbonin et al., 1991).

An analysis of 48 cohort studies found the overall age-standardized relative risk of an adverse drug reaction in females compared with males was 1.6 (95% CI = 1.5-1.7) (Martin, Biswas, Freemantle, Pearce, & Mann, 1998). This study was limited to prescriptions of newly marketed medications in England but, nonetheless, it reflected a difference between the sexes across all age groups over 19 years old.

While age and sex appeared to play a role in the risk for an adverse drug reaction, neither variable appeared to be an independent risk factor once adjusted for the effects of other variables. The number of medications became a risk factor that was repeatedly reported as being a stronger predictor of adverse drug reactions after adjusting for age and sex.

Polypharmacy as a risk factor for adverse drug reactions

In the days of individually compounded medications, polypharmacy was simply the mixing of many drugs into one prescription (Colley & Lucas, 1993). Today, polypharmacy has been interpreted as an excess and unnecessary use of medications or simply the use of multiple medications (French, 1996; Hanlon et al., 1997; Manasse, 1989). Prescribing practices that may indicate polypharmacy included a) prescribing medications that have no apparent indication, b) use of duplicate medications in the same drug category, c) concurrent use of interacting medications, d) prescribing drugs contraindicated for use among the elderly, e) ordering inappropriate dosages, f) using a drug to treat an adverse drug reaction, and g) clinical improvement following discontinuation of medication (French, 1996).

Attempts were made to assess the association between polypharmacy and adverse drug reactions in an elderly outpatient population (Veehof et al., 1999). Medication and morbidity data on patients older than 64 years were collected from three family practice clinics in the Netherlands. Defining polypharmacy as the long-term simultaneous use of two or more appropriately prescribed drugs, this group did not confirm an increased risk of adverse effects with the number of drugs used simultaneously. This was one of the few studies that failed to find an association between polypharmacy and adverse drug reactions. This might be explained by the restriction of the polypharmacy definition to long-term use. Long-term was designated as 480 days or more in 2 years and adverse effects were restricted to only the ones observed and registered by the physician. Yet, even when Gandhi used less restrictive terminology in a self-reported survey, the multivariate analyses yielded a nonsignificant association between the number of medications and drug complications (Gandhi et al., 2000).

Polypharmacy, that is, taking two or more appropriately prescribed drugs concurrently, was associated with an increased risk of adverse drug reaction mortality. A study using medical records, lab tests, autopsy findings, and detailed information on drug use to assess drug-related deaths and to search for patient characteristics associated with an increased risk of a fatal adverse drug event, found a significant association between the number of drugs used and the risk of drug-related death (Ebbesen et al., 2001). In this study, 728 patients died in the hospital. Of those who died, 202 patients used 12 or more drugs at the time of death. Of these 202 deaths, 48 (23.8 percent) were classified as drug-

related. In the remaining 526 deaths of patients who were using fewer than 12 drugs at time of death, 85 (16.2 percent) were considered drug-related.

It made intuitive sense that sicker patients would take more medication and, therefore, sicker patients would be more likely to die, but the researchers did try to account for this whenever possible (Ebbesen et al., 2001). For example, although large doses of drugs used for pain relief may have shortened life slightly, these drugs were considered necessary for palliation and were not classified as causing a fatal event.

Overall, the majority of studies that assessed the association between the number of prescriptions and the risk for adverse drug reactions reported an increased risk with an increasing prescription count. This incidence of adverse drug reactions reportedly increases exponentially rather than linearly with the number of drugs (Nolan & O'Malley, 1988). This exponential association suggests that a relatively small reduction in the medication regimen can have a profound effect on the relative risk for an adverse drug reaction (Atkin & Shenfield, 1995). They are not simply additive for several reasons. The foremost reason is that sicker people take more drugs and, conversely, those patients who are sicker may experience disease symptoms that are erroneously attributed to drug treatment.

It was also suggested that drug interactions might play a part in this phenomenon since rates of reactions to individual drugs were dependent upon the number of drugs given concurrently (May, Stewart, & Cluff, 1977). Drug interactions could be antagonistic, synergistic, or idiosyncratic (Jankel & Fitterman, 1993). A drug-drug

interaction was usually considered to result in a negative outcome but this was not always the case.

A study of potential drug-drug interactions in coronary heart disease and chronic obstructive lung disease patients found that the number of potential interactions was significantly correlated in a polynomial manner to the number of drugs taken by each patient (Kohler et al., 2000). Most (68 percent - 70 percent) of the potential drug interactions would necessitate attention of the prescribing physician and as many as 1 percent to 2 percent were judged potentially life-threatening. Between 17 percent and 18 percent of the interactions could actually have been therapeutically beneficial.

Finally, drugs used to treat adverse reactions and their resultant adverse effects will contribute to the number of drugs and to the association (Nolan & O'Malley, 1988).

"Multiple pathology is an invitation to polypharmacy" (Beard, 1992). It is uncommon to find studies that attempt to correlate the number of prescriptions with the number of diseases and the risk of an adverse drug reaction.

Multiple pathologies as a risk factor for adverse drug reactions

Studies that assessed co-morbidities as a predictor of adverse drug reactions tended to find them statistically significant contributors after adjusting for other variables such as age, sex, and concomitant medication. Adjusting for disease severity was one of the elements that influenced the association between age and adverse drug reactions.

Both the number of medications and the number of medical problems were significant clinical correlates of patient-reported drug complications in the univariate analyses in Gandhi's study (Gandhi et al., 2000). Only the number of medical problems

remained an independent clinical correlate of patient-reported drug complications in the multivariate logistic regression analysis (OR 1.17: 95% CI = 1.05-1.30). Contrary to Gandhi's results, Carbonin's group found that both taking more than four drugs (OR = 2.94, 95% = CI 2.38-3.62) as well as having more than four medical problems (1.78, 95% CI = 1.29-2.45) remained significant predictors of total adverse drug reactions (Carbonin et al., 1991).

The altered drug handling capacity caused by some existing illnesses is well known (Bates et al., 1999; Cadieux, 1989; Young, Wurtzbacher, & Blankenship, 1997). The pharmacodynamic and pharmacokinetic changes resulting from renal insufficiency, hepatic insufficiency, and congestive heart failure can predispose patients with these conditions to an increased risk of an adverse drug reaction. Some authors reflected that the slight alteration in hepatic function with age had little clinical significance, but that changes in the volume of distribution were more relevant. An increase in volume of distribution prolongs plasma elimination half-life and the duration of drug action (Nolan & O'Malley, 1988).

Multiple physicians as a risk factor for adverse drug reactions

> The ideal physician-patient ratio is often 1. Does that mean there is no room for consultation or the management of distinctive problems by different specialists? Cannot each respect the other's turf? Probably so, but still there needs to be a head coach, a pharmaceutical gatekeeper controlling the patient's regimen. Where multiple voices cry out, one doctor must moderate the assembly (Kroenke, 1985).

Kroenke's view that "polyphysicianism", that is, more than one prescribing physician involved in a patient's care, contributes to polypharmacy makes theoretical

sense. Little has been done to empirically test whether multiple physician prescribing played a significant role in adverse drug reactions.

In a study on the role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly, researchers found that the greater the number of physicians seen regularly, the greater the risk of hospitalization for noncompliance (OR 2; $p = 0.005$) (Col et al., 1990). They did not report finding significance in those admitted for adverse drug reactions.

A cross-sectional retrospective database study looked at two measures of physician involvement: prescribing physicians and number of physicians providing care (Tamblyn, McLeod, Abrahamowicz, & Laprise, 1996). For this study they restricted their review to three drug classes: nonsteroidal anti-inflammatory drugs (NSAIDs), cardiovascular agents, and psychotropic agents. They reported that the number of prescribing physicians was more strongly associated with the risk of a potentially inappropriate drug combination than the number of physicians providing medical care. For cardiovascular drug combinations, the risk of a potentially inappropriate drug combination increased by 71 percent for each doubling in the number of prescribing physicians, by 45 percent for NSAIDs, and by 44 percent for psychotropics. In contrast, when the number of physicians providing medical care doubled, these risks were lower at 39, 17, and 21 percent, respectively, implying that the risk was due to the number of physicians prescribing, not the number of physicians consulting on the medical problem. These results appeared to support Dr. Kroenke's call for a pharmaceutical gatekeeper.

Who should be the pharmaceutical gatekeeper? If not the physician, could this role be played by the pharmacists who fill the prescriptions?

Multiple pharmacy use as a risk factor for adverse drug reactions

One study attempted to determine the proportion of hospital admissions that were secondary to noncompliance and adverse drug reactions and assess their causes and predictors (Col et al., 1990). A factor that was unique to this study was their assessment of an association between the number of pharmacies patients used and the prevalence of adverse drug reactions. They found that patients using two or more pharmacies had a higher prevalence of adverse drug reactions (15.8 percent) than those who used only one (12.1 percent)

While this difference was not statistically significant, it posed an interesting concept within the context of adverse drug reaction studies. Especially with the sophisticated pharmacy databases that can screen for drug-drug interactions and patient allergies, the use of a single pharmacy could be one of the best methods of adverse drug reaction prevention that is completely under the patient's control.

Miscellaneous risk factors for adverse drug reactions

Hurwitz reported that a significantly higher percentage of patients with adverse drug reactions had a history of a previous reaction (Hurwitz, 1969b). Likewise, Cadieux's review and Hutchinson and colleagues also singled out previous allergic or idiosyncratic reactions as a factor that could contribute to future adverse drug reactions (Cadieux, 1989; Hutchinson et al., 1986).

Genetic differences in drug metabolism may predispose certain patients to an adverse drug reaction (Ajayi et al., 2000; Meyer, 2000). The genetic variability in drug-metabolizing may result in poor metabolizers or ultrarapid metabolizers and may explain the unexpected toxicities after a therapeutic dose.

Drug and therapeutic class specific adverse drug reactions

Often, it was not merely the number of drugs the patient took that put them at greater risk for an adverse drug reaction but rather the specific drug or therapeutic class of drug they took. A study of nine index drugs found that not only was there a greater risk of adverse drug reactions in taking multiple drugs but this risk was also increased by the type of drugs taken (May et al., 1977). This group found that the average number of adverse drug reactions for the anticoagulant and antihypertensive drug groups was higher ($p < 0.05$) than for all other drug groups when classified by the number of drugs being taken concurrently.

It should be noted that many studies excluded antineoplastic drugs because their toxicities were well known, expected, and often accepted as a customary trade-off for which the potential benefits far exceeded the risks. These agents could potentially make up a large proportion of the reported reactions. For example, Fattinger reported that adverse drug reactions caused 3.3 percent of 4,331 hospitalizations but if cancer-chemotherapy-induced leukopenia were excluded, the rate was reduced to 2.7 percent (Fattinger et al., 2000). Since the side effects of antineoplastic therapy can result in office visits, emergency department visits, hospital admission, additional drug treatment to prevent and/or counter the adverse effects, dose modifications based upon the adverse

effects, and increased mortality due to the adverse immunosuppressive and hematological effects, it can be argued that this exclusion is inappropriate.

The results of Roughead's study using ICD-9-CM coding seemed to concur. This study identified antineoplastic and immunosuppressive drugs, penicillins, hypertensive agents (beta-blockers, diuretics, and coronary vasodilators), corticosteroids, anticoagulants, cardioglycosides, and antirheumatics (NSAIDs and gold salts) in descending order as the drug classes most commonly indicated in drug-related hospital separations (Roughead, 1999).

The study of emergency department visits in a health maintenance organization (HMO) reported the top three most common drug classes causing medication misadventures were anti-infectives (23.6 percent), analgesic agents (23.3 percent), and cardiovascular agents (18.5 percent) (Schneitman McIntire et al., 1996). Adverse drug reaction studies in children tended to report anti-infectives (including vaccines) as the most frequent class of drugs causing adverse reactions in the pediatric population (Martinez-Mir et al., 1999; Menniti-Ippolito et al., 2000).

A subcategory of adverse drug reactions that was infrequently delineated in the reports of the adverse drug reaction studies was that of drug interactions. Drug-drug interactions can be antagonistic, synergistic, or idiosyncratic (Jankel & Fitterman, 1993). Concurrent prescribing of potentially interacting drugs is common and becomes complicated to interpret because often the indications for the drugs may themselves be the cause of an increased risk of adverse outcomes (Hamilton, Briceland, & Andritz, 1998). If comparisons are made solely between those hospitalized after receiving a

combination of potentially interacting drugs and those not receiving either drug, the chance of reaching statistical significance is greater. Using Medicaid claims data, Hamilton and colleagues evaluated the influence of a drug-drug interaction compared to the use of a single drug. This technique was used to control for the background risk of hospitalization secondary to the indication for the drug.

Of 28 drugs and/or drug classes studied by Hamilton and colleagues, three classes had background risks that were protective, one class had no effect, and the remainder demonstrated an increased risk for hospitalization when used individually. When the drugs were combined, 23 of the 141 interactions considered showed a statistically significant greater risk of hospitalization with the combination versus the individual agents.

While drugs that can potentially interact with each other are still often prescribed in combination, there is a growing amount of literature discussing the appropriateness of medication prescribing in combination and by drug-disease state interactions. Beers provided an update of potentially inappropriate medication use in patients 65 years or older with specific disease conditions (Beers, 1997). The expert panel involved in this review identified 28 criteria describing potentially inappropriate use of medication in the general population of older persons, as well as, 35 criteria that described inappropriate use in older persons with any of 15 common medical conditions.

Similarly, a Canadian consensus panel elaborated on several criteria for assessing the appropriateness of prescribing practices (McLeod, Huang, Tamblyn, & Gayton, 1997). Prescribing was considered inappropriate when three criteria were met. First,

initiating the prescription increased the risk of a clinically serious adverse effect. Second, equally or more effective and less risky alternative therapy was available. Third, the practice was likely to occur often enough that changing the practice could decrease morbidity. The emphasis in this study was on the contraindications between drugs and disease states prominent in the older population. The combination of these criteria could be used to identify those persons potentially at an increased risk of adverse drug reaction.

While drug interactions are important, their contribution to the overall frequency of adverse drug reactions was minimal in most of the adverse drug reaction studies and varied little among the inpatient and outpatient studies. Frequencies of drug-drug interactions reported as a contributor of adverse drug reactions ranged from 0 to 4 percent (Grymonpre et al., 1988; Hallas et al., 1992; Koecheler Schneider et al., 1992; Lakshmanan et al., 1986; Larmour et al., 1991; Prince et al., 1992; Steven, Malpass, Moller, Runciman, & Helps, 1999). Although the frequency of drug-drug interactions appeared to be low, this does not mean that they did not have the potential to be serious. Kelly reported that among the 447 cases involving fatal adverse drug events, 6 percent were attributed to drug interactions (Kelly, 2001a). Likewise, among 227 cases of drug-induced permanent disabilities, 2 percent were attributed to drug interactions (Kelly, 2001b).

The drug-drug interactions most often cited involved digoxin, warfarin, or NSAIDs. The addition of an interacting drug to these three agents frequently caused a hospital admission due to either digoxin toxicity or gastrointestinal bleeding (Larmour et al., 1991). Consideration must be given to how an adverse drug reaction is most likely to

manifest. This becomes important in building suspicion that the drug was the culprit rather than the disease or some other factor.

Manifestation of adverse drug reactions

A retrospective evaluation of 612 adverse drug reactions that had occurred in a hospital over a 4-year period found that 30 percent of the reactions were allergic-type reactions (Seeger, Kong, & Schumock, 1998). This was followed by neurologic (13 percent), gastrointestinal (12 percent), hepatic or renal (11 percent), hematologic (9 percent), and cardiovascular (8 percent) reactions. The remaining six categories were all five percent occurrence or lower. These types of reactions seemed to correspond well with the drug classes that were the most frequently recorded as causes of adverse drug reactions in their study: antibiotics (26 percent), central nervous system agents (23 percent), and cardiovascular agents (11 percent). These types of adverse responses are within the realm of plausibility of being caused by these agents.

The reports of hospital admissions partially mirrored Seeger's inpatient results. When medication misadventures were studied in a HMO emergency department, the primary diagnoses for patients admitted to the hospital due to medication problems were gastrointestinal bleeding (37.5 percent), digoxin toxicity (6.6 percent), and drug allergy (4.6 percent) (Schneitman McIntire et al., 1996).

The primary diagnoses recorded in this outpatient study that caused the emergency department visit diverged somewhat from the inpatient and hospital admission studies. Allergic responses remained the most frequently reported primary diagnosis at 20.6 percent of patients followed by intolerance (9 percent), central nervous system

effects (7.8 percent), exacerbation of asthma or chronic obstructive pulmonary disease (6.6 percent), gastrointestinal bleeding (6.6 percent), hypo or hyperglycemia (6.2 percent), and gastritis (5.2 percent). The remaining categories all involved less than 5 percent of the patients. Whereas digoxin toxicity was a frequent factor for inpatient and hospital admissions, only 2 percent of the patients in this outpatient study suffered from this adverse reaction but recall that 6.6 percent of admissions due to drug misadventures were secondary to digoxin toxicity. Like the inpatient and hospital admission studies, the drug classes that were implicated most frequently were those that would be expected to cause the adverse reactions that were experienced. Thus, it should not be surprising that antibiotics (23.6 percent of cases), analgesics (23.3 percent), cardiovascular agents (18.5 percent) respiratory agents (8.7 percent), and hypoglycemic agents (6 percent) were the most frequently recorded drug classes in this study.

When the population of interest was narrowed to high risk older outpatients as in Hanlon's study at a Veterans Administration medical center, the reactions shifted away from the allergic reactions and appeared to center more on gastrointestinal (30 percent) and central nervous system (28.8 percent) reactions that predominantly involved the cardiovascular (33.3 percent) and central nervous system (27.8 percent) medication classes (Hanlon et al., 1997). Chrischilles' group concurred with 29.1 percent of their 65 years and older sample experiencing gastrointestinal reactions and 26.2 percent experiencing central nervous systems reactions; however, analgesics played a more prominent role with 22.2 percent of the patients attributing the adverse reactions to this drug class (Chrischilles et al., 1992). Combined with cardiovascular agents with 32.4

percent of patients, these two drug classes accounted for over 50 percent of drug classes to which respondents attributed their adverse drug reactions. Additional outpatient studies yielded results consistent with these studies (Gray et al., 1999; Stoukides et al., 1993).

Not only are there physical and emotional ramifications from an adverse drug reaction but there are also financial costs associated with the assessment and treatment of these effects.

Adverse drug reaction-associated costs

Much of the literature reporting estimates of the economic ramifications of adverse drug reactions in an ambulatory population used cost-of-illness decision tree modeling (Bootman, Harrison, & Cox, 1997; Ernst & Grizzle, 2001; Johnson & Bootman, 1995). The 1995 estimate of $76.6 billion was recently updated and reported that the overall cost of drug-related morbidity and mortality was estimated to be $177.4 billion in 2000. These models included eight negative outcomes of drug therapy: untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs, overdosage, adverse drug reactions, drug interactions, and drug use without indication.

Some of these categories would not be considered under the definition of adverse drug reaction by many of the adverse drug reaction studies, but the cost-of-illness models provided a picture of what elements of drug-related morbidity and mortality treatment were accounting for most of the costs. The bulk of the costs were hospital admissions (68.5 percent), followed by long-term-care facility admissions (18.5 percent), physician

visits (7.8 percent), emergency department visits (3.2 percent) and additional prescriptions (2 percent) (Ernst & Grizzle, 2001). A 1997 model on the health care cost of drug-related morbidity and mortality in nursing facilities estimated that for every dollar spent on drugs in nursing facilities, $1.33 in healthcare resources were consumed in the treatment of drug-related morbidity and mortality (Bootman et al., 1997).

There are few studies that empirically looked at the costs associated with adverse drug reactions. Those studies that did were more likely to be estimated from a hospital perspective (Classen et al., 1997; White, Arakelian, & Rho, 1999). A group that examined the costs of adverse drug events in hospitalized patients concluded that the costs attributable to an adverse drug event were $2595 per adverse drug event (Bates et al., 1997). Extrapolating these single-event costs to their 700-bed teaching hospital, they estimated the annual costs to be $5.6 million. Adverse drug events in this study were defined as injuries resulting from medical intervention related to a drug; therefore, drug errors were included.

Moore spoke about the "ransom of progress" (all drugs are dangerous, some are also useful) when he discussed the fact that once an adverse drug reaction was known and included in product information, they tended to drop off the radar screen as far as reporting and tracking their occurrence and costs (Moore, 2001). However, as he goes on to eloquently argue, these commonplace types of reactions represent the vast majority of serious drug reactions, can often be avoided, and represent the real risk and cost of drugs to society.

An analysis of drug expenditures in patients with cancer in the Hospital of the University of Pennsylvania illustrated Moore's point (Gibson, 2000). Over 50 percent of the average $2074 per patient drug expenditures in patients with cancer in that facility was associated with treating chemotherapy-induced adverse reactions. That figure was just the drug expenditures. Adverse drug reactions also contributed to office visits, emergency department treatment, and hospital admission costs as well as to a myriad of additional indirect costs.

A study of 167 older, high risk outpatients found that 84 percent of the 58 patients who experienced an adverse drug reaction required health care services of some sort to assess or treat the reaction (Hanlon et al., 1997). Ten percent of those who experienced an adverse drug reaction received emergency room treatment, 11 percent required in-hospital care, and 63 percent required physician contacts.

These results compare to a larger Iowa survey of 3,170 noninstitutionalized persons 65 years and older (Chrischilles et al., 1992). They found that 75.2 percent of the 318 respondents reporting an adverse drug reaction consulted a physician about the reaction. Hospitalization occurred in 7.1 percent of the cases. Dose modification or elimination was needed in 68.2 percent of the cases and labs were ordered in 50.6 percent of the cases.

One consequence of an adverse drug reaction that cannot be easily assessed was what happened in those patients who did not contact their physician about their drug-related problems. In the 69 patients who did not contact a physician, 56.5 percent stated they quit taking the drug. The ramifications of an untreated condition go beyond the

scope of this document but the financial costs were estimated in the cost-of-illness models mentioned previously (Ernst & Grizzle, 2001; Johnson & Bootman, 1995).

Claims database use in research

"Automated databases are typically established for record management and financial purposes (Faich & Stadel, 1989)." Electronic linkage of pharmacy, physician, hospital, and other healthcare databases will be key to producing useful outcomes-oriented data sets (Miller, Blatman, & Einarson, 1996). The advancement of computer technology and the accessibility to the wealth of information in these warehoused databases resulted in an increased popularity of database research.

The appropriateness of whether a database can or should be used for a study depends on the research goal (van Eijk, Krist, Avorn, Porsius, & de Boer, 2001). The source of the data will dictate what elements are available for study but the key components of most managed care organization data warehouses are medical claims, pharmacy claims, member eligibility data, and provider data (Armstrong & Manuchehri, 1997).

Database elements

The perfect database does not exist but the following elements would contribute to the ideal database (van Eijk et al., 2001):

1) Ability to follow persons (patients and providers) over time

2) Registering all encounters and the identity of the provider(s) involved

3) Having all persons uniquely coded

4) Supplying a clear mapping relating old codes to new ones

5) Containing unambiguous terminology

6) Collecting as many patient characteristics, for example, smoking or alcohol use, as possible

7) Reporting relevant details about all health care services

8) Reporting episodes of care rather than independent encounters

9) Reporting information on severity of illness

10) Providing methods of linking information between databases

11) Security, accuracy, and continuity

An advantage of database studies is their potential ability to follow people over long periods of time making them useful for longitudinal studies on chronic diseases (Lewis, Patwell, & Briesacher, 1993; Motheral & Fairman, 1997). The completeness of the information hinges on the database being used. For example, Medicaid beneficiaries enter and leave beneficiary status based upon income fluctuations. HMO beneficiaries generally have a definitive enrollment period but patient switches between plans may occur annually nor is this information necessarily obtainable from the database.

For many reasons, beneficiaries or providers may not file a claim so the researcher can never be assured that all encounters are actually in the database. The extent of the missing encounters can be influenced by the drugs or procedures that are excluded from coverage as well as those that are not submitted because the plan

deductibles were not met. The omission of over-the-counter (OTC) drugs, drug samples, and drugs received as an inpatient are important elements that must be considered when using prescription claims data to assess drug exposure. The amount of care received outside the healthcare system is also a potential problem for database researchers (Strom & Carson, 1990).

The majority of provider information in the databases appeared to be accurate. Tamblyn's group tested the completeness and accuracy of prescription database information when they matched records from a prescription claims database in Quebec with the clinic files of 306 elderly patients from an internal medicine clinic and found that physician information was correct 89 percent of the time (Tamblyn, Lavoie, Petrella, & Monette, 1995).

Unique coding of each beneficiary was an issue when dependents of the sponsor had medical encounters coded against the sponsor instead of the individual. A family code may be sufficient for reimbursement but it stymies the researcher. Although the family data might be combined with a date of birth and sex to identify an individual, this is not possible in some instances, for example, same-sex multiple births. In addition, combining this type of information creates an opportunity for errors. Pharmacies and physicians require unique codes to identify multiple pharmacy and multiple physician use.

Recycling of identifier information can occur without the researcher's knowledge. Even if the code itself were not changed, changes in reimbursement can alter coding patterns and affect the frequency of use (Motheral & Fairman, 1997).

The use of ICD-9-CM codes, physician's Current Procedural Terminology (CPT) codes, and Diagnostic Related Group (DRG) are important to reimbursement but they have well known and unique deficiencies when applied to database research (Iezzoni LI, 1997). Coding errors and improper coding can lead to false-positive codes (misclassification) (Armstrong & Manuchehri, 1997) and affect reimbursement (Lloyd & Rissing, 1985). Coding biases may also occur when acute conditions or complications take precedence in coding over chronic conditions (Iezzoni et al., 1992).

The absence of information on confounding variables is one of the greatest challenges in using automated databases in research (Collet, Schaubel, Hanley, Sharpe, & Boivin, 1998). For example, while an exposure to an NSAID and the experience of a gastrointestinal bleed are detectable within pharmacy and medical claims databases, the patient's exposure to other contributing factors, such as alcohol, are not. A study using Medicaid billing data to assess the feasibility of studying drug-induced acute hepatitis found that the Medicaid database had a high reliability and validity for the diagnosis of acute liver disease but that once records were reviewed, 15.9 percent of patients were found to be alcoholics and an additional 57.7 percent had other causes of their liver disease (Carson et al., 1992).

Ideally details about all health care services, including test results, diagnosis, time, place, costs, patient, and provider would be available in the database. Because these are administrative databases, there is no incentive to submit details beyond that which is required to obtain reimbursement. Databases cannot tell the investigator what might have affected the physician's decision to prescribe a drug nor whether the

diagnosis was accurate and complete nor do they contain much data that could assist in the analysis of clinical outcomes (Armstrong & Manuchehri, 1997; Edlavitch, 1988). It is especially difficult to identify specific laboratory tests using claims data because lab work is billed using package codes that vary between facilities (Motheral & Fairman, 1997). Most claims databases only indicate a lab test was performed; results are typically not included (Armstrong & Manuchehri, 1997).

Especially for outpatient services, it is often difficult to track whether one encounter resulted in the order of more services or referrals. A prescription claim can only be associated with a medical encounter based upon the proximity of the service dates (Armstrong & Manuchehri, 1997).

Most coding in the administrative databases provides evidence that the disease is present but provides no information about how rapidly the disease developed or progressed nor does it contain any other information about severity of illness. This is a well noted limitation of administrative databases (McMahon & Smits, 1986).

There must be a unique identifier to allow for cross-linkage between databases for the differing healthcare services. The patient identifier is the most feasible data point for linking the information. Because the information found in these databases is sensitive health information, accessibility to it is limited to authorized personnel. For research purposes, the patient identifiers may be removed or replaced with an encrypted number to allow linking between records while maintaining patient privacy.

Design issues with database studies

Concurrent with the elements of the database, however, is the validity of the study design used to incorporate these elements. In a critique of automated record linkage, researchers were reminded that the basic elements of causal research needed to be considered in claims database research (Shapiro, 1989). These factors included a properly defined exposure and outcome with an exposure that antecedes the outcome, duration and time interval of exposure that is relevant to the hypothesis, a method to control for bias and confounding, and coherence in a dose-response and duration-response relationship. The strength of the association and its consistency with other investigators also lends support for causality (Hennekens & Buring, 1987c; Shapiro, 1989).

The advancement and usefulness of claims database research is dependent in part upon the accuracy and completeness of the data but considering that medication histories are often incomplete and patient recall inaccurate (West et al., 1995), database records of dispensed prescriptions may be the most accurate way of assessing drug utilization in a population (Tamblyn et al., 1995). A study testing the completeness and accuracy of a prescription database found that the values in key fields such as patient identifiers, drug, quantity, date dispensed, and duration were missing or out of range in only 0 to 0.4 percent of records (Tamblyn et al., 1995). Physician information was correct 89 percent of the time, quantity 69.1 percent, and duration 72.1 percent. They concluded that the prescription drug database provided reasonably accurate information on the drug

prescribed and the prescribing physician in their test population but that it had some limitations if using it for dosing information.

Researchers need to consider whether an exposure recorded in a database was a true exposure (Strom & Carson, 1990). Researchers attempting to assess drug exposure with a prescription claims database as compared to the gold standard patient home interview concluded that prescription databases could be reliable sources of true drug exposure (Lau, deBoer, Beuning, & Porsius, 1997). Complete and accurate automated pharmacy data can be a cost-efficient record of drug intake (Jick & Walker, 1989). Although pharmacy database studies are useful for establishing drug exposure, they hinge upon the assumption that a drug dispensed was actually taken. It is also presumed that a patient was not exposed to drugs not on the dispensing list (Jick, Jick, & Derby, 1991). This is a troubling assumption since many pharmacy databases do not include over-the-counter medications nor can it take into account the sharing of medications or medication samples. Misclassification of exposure is expected to be random but, nevertheless, remains a threat to the internal validity of a database study if the misclassification is occurring systematically (Motheral & Fairman, 1997; Strom & Carson, 1990).

Another element when matching prescription database information with medical files is the time delay from prescription order to claims processing. This aspect was addressed when medication data from nursing home residents were matched against a prescription claims database. By using nursing home medication records, the problem with patient recall was negated. The researchers found that the best matching between the nursing home records and the prescription database reached a plateau within 12

weeks (King, Purdie, & Roberts, 2001). The time element also plays a role in that most database studies are limited to exploring associations between an illness and current drug use when it may require long-term exposure to produce the illness (Strom & Carson, 1990).

The ability to assess an outcome is as important as the ability to accurately assess drug exposure. Whereas a physician may not know about care the patient received from other physicians, claims data have an advantage in that virtually all medical care is recorded (Strom & Carson, 1990). In a study that attempted to identify hypertensive patients, the authors found that using criteria that incorporated pharmacy claims and medical claims provided a stronger concordance with the medical record than did relying upon either claim set alone (Quam et al., 1993). If the illness of interest is one that is unlikely to appear in the database, then it cannot easily be studied using claims data (Strom & Carson, 1990). For example, it would not be easy to study the occurrence of minor skin rashes with a claims database because these rashes do not usually require medical treatment.

Study of a disease that can result in a high frequency of rapid death before being hospitalized may be inappropriate for a claims database study because it would miss a significant number of cases (Strom & Carson, 1990). Death from an illness is difficult if not impossible to capture with claims data alone.

There are a number of advantages and disadvantages to the case-control design used in observational database studies (Newman, Browner, Cummings, & Hulley, 2001). Because the selection of a case is based upon disease status, a case-control design has

particular advantages in the evaluation of rare events like adverse drug reactions, which showed a range of 0.05 percent to 41 percent occurrence among outpatient studies (Table 2). A case-control design also allows for evaluation of a wide range of potential etiologic exposures that might be associated with the outcome (Hennekens & Buring, 1987a).

A major disadvantage to the case-control design is its susceptibility to bias and confounding. Sampling bias can occur when the cases are unrepresentative with respect to the risk factor being studied (Newman et al., 2001). The potential selection that preceded the diagnosis could influence the results. For example, if those with a higher number of co-morbidities were selectively given quicker access to care and if selection of cases were dependent on an encounter claim within 30 days of drug exposure, the subsequent claims data from a healthcare encounter could over-represent those with a greater number of co-morbidities because they had an increased opportunity of getting selected as cases due to the imbalance in access in care.

Matching is one method of controlling for confounding in case-control studies. A limitation of matching is the inability to evaluate the effect of a factor that has been matched for on the risk of the outcome (Hennekens & Buring, 1987b). For example, if cases and controls are matched on age, then the effect of age on adverse drug reactions can not be assessed. Frequency matching is one way to control for confounding on one level while still allowing the assessment of the association between the predictor and the outcome. Frequency-matching entails matching the controls to the cases within a stratum of the potential confounding variable. For example, if 30 percent of the cases were between 50 and 60 years old, then 30 percent of the controls should be between this age

range. Because the subjects are not matched on a patient-level basis, the effects of the confounder (age) can still be assessed with multivariate techniques.

Claims database use in assessing adverse drug reactions

Claims databases have been used to identify adverse drug reactions due to individual drugs or drug classes. For example, studies were done examining the association between psychotropics and hip fracture risk (Ray, Griffin, Schaffner, Baugh, & Melton, 1987), allopurinol and cataracts (Jick & Brandt, 1984), and nonsteroidal anti-inflammatory drugs in relation to upper gastrointestinal bleeding (Carson, Strom, Soper, West, & Morse, 1987). The use of claims data in this manner generated heated debate because of some of the questionable study designs that were used (Faich & Stadel, 1989; Shapiro, 1989; Strom, 1989).

This debate was best illustrated in a critique of automated record linkage studies (Shapiro, 1989). He cited, for instance, a study derived from automated prescription and discharge data that looked at the association between allopurinol exposure and cataracts (Jick & Brandt, 1984). The exposure in this case was defined as anyone receiving a prescription for allopurinol in a given year, whereas the outcome was identified by cataract surgery. At issue is the fact that a short term exposure to allopurinol could not plausibly induce cataract development: a process that normally takes years. The argument was also raised that the chosen outcome was inappropriate because the hypothesis was that allopurinol caused cataracts, not cataract surgery (Shapiro, 1989). In addition, there was no control for the confounding of other cataract-causing risk factors.

One study that was able to meet most of the criteria using only automated data was done in a Medicaid population (Ray et al., 1987). The researchers looked at psychotropic drug use and the risk of hip fracture. The categories of exposure included the short half-life (< 24 hours) hypnotics-anxiolytics, long half-life (> 24 hours) agents, tricyclic antidepressants, and antipsychotics. The outcome of hip fracture was found through the use of an ICD-9-CM code and was validated against coded procedures. They controlled for the confounding of dementia and included only those with continuous Medicaid enrollment.

Drug benefit claims data were used to assess for potentially inappropriate drug selection using the explicit criteria outlined by Beers' group (Anderson, Beers, & Kerluke, 1997). This analysis used the Pharmacare claims data from the British Columbia Ministry of Health to look at prescribing physician characteristics for specific agents within four drug classes: antidepressants (amitriptyline), nonsteroidal anti-inflammatory drugs (indomethacin, phenylbutazone), sedative hypnotics (chlordiazepoxide, diazepam, and flurazepam), and oral hypoglycemics (chlorpropamide). They found that their percentage of eligible population exposed to potentially inappropriate medications was similar to that of an American study that used information from the National Medical Expenditure Survey (NMES) to assess inappropriate drug prescribing (Willcox, Himmelstein, & Woolhandler, 1994). Both studies used data collected in the late 1980s. Despite the different study methods, the results were very similar: amitriptyline use was 2.6 percent versus 3.13 percent with NMES; long-acting sedative hypnotics use was 5.8 percent versus 6 percent with NMES;

NSAID use was 4.6 percent versus 3 percent with NMES; and chlorpropamide use was 1 percent versus 2 percent. Their similarities indicate a good potential for using claims data as a screening tool for inappropriate prescribing.

This claims database study was interesting in that the researchers were able to identify characteristics of the prescribing physician that might predict poorer prescription practices. The authors thoroughly acknowledged that this administrative data did not provide detailed clinical characteristics of the patients; therefore, this audit should not be used to provide a definitive assessment of quality of care. Because the criteria used in this study did not measure outcomes, the authors could not know whether the benefits outweighed the risks of use in a particular patient. Yet, if the emphasis of this type of study is placed on its indicator ability, this type of audit could be a useful screening mechanism not only for identifying patients at risk for experiencing adverse events due to potentially inappropriate prescribing, but also identifying prescribing physician practices that are potentially putting patients at unnecessary risk.

A limitation of database studies in general is that physicians are more likely to record the primary diagnosis, that is, if they are treating an acute illness, they may not record any chronic illnesses the patient has (Strom & Carson, 1990). This database limitation may actually result in a greater opportunity of finding adverse drug reactions within the database since the majority of reported adverse drug reactions occurred within a short time after drug initiation.

The source of the information used in any claims database study will be a factor in determining what kind of questions can be researched. Understanding the elements

that are unique to the healthcare plan under which the claims are being submitted is important in establishing the limitations of the research.

TRICARE Healthcare Program

The Department of Defense (DoD) provides medical and pharmacy benefits to DoD beneficiaries through the TRICARE healthcare program. In 2001 the DoD TRICARE program covered 8.2 million lives: 1.6 million active duty personnel, 2.3 million active duty dependents, and 4.3 million retirees (1.3 million over age 65). TRICARE does not decide who is eligible for health care benefits. Eligibility records are maintained in the Defense Enrollment Eligibility Reporting System (DEERS) database. Active duty and retired military members are listed in DEERS automatically but they must actively seek addition or deletion of family members (TRICARE Support Office, 1997).

The management of the TRICARE program is the responsibility of the TRICARE Management Activity (TMA) office. Within the continental United States, the TMA divides the delivery of healthcare to DoD beneficiaries among 11 regions. Each region is assigned a Lead Agent, usually located at the largest military treatment facility (MTF) in the region, responsible for the development, execution, and evaluation of its regional managed care support contracts. The Lead Agent is the oversight authority between the MTFs and the regional managed care support contractors. Working in tandem, these organizations meet the healthcare needs of DoD personnel within their regions. Each eligible DoD beneficiary has three options for their medical benefits.

TRICARE medical benefits

1) TRICARE Prime – an HMO-type option in which a beneficiary must enroll and select a military or civilian primary care manager (PCM) from whom to seek their health care. TRICARE Prime has the lowest out-of-pocket costs when beneficiaries use their assigned PCM. Use of providers who are not TRICARE Prime providers costs extra. Enrollment periods were for one year with automatic re-enrollment unless actively declined by the member.

Enrollment fees: TRICARE Prime was free for active duty members and their families. Retirees and their families paid an annual fee of $230 per person or $460 per family.

Deductibles: None.

Treatment Costs: Outpatient treatment in a MTF was free while inpatient treatment was $11 per day. Outpatient treatment in a civilian facility cost $6 or $12 depending on the sponsor's rank. There was a $25 minimum in civilian facilities.

Provider Choice: Care was generally provided by the MTF but when not available would be given by civilian providers.

2) TRICARE Standard – replaced the CHAMPUS (Civilian Health and Medical Program of the Uniformed Services) Program. TRICARE Standard is a fee-for-service, indemnity health care option and the most costly of the three available options. Active duty personnel were not eligible for TRICARE Standard and were automatically enrolled in TRICARE Prime.

Enrollment fees: None. Enrollment was not required.

Deductibles: Based upon the rank of the military sponsor.

E-4 and below: $50 per person per fiscal year

E-5 and above: $150 per person per fiscal year

E-4 rank is equivalent to an Air Force Senior Airman, Navy Petty Officer Third Class, Army specialist/corporal, and Marine corporal. E-5 rank is equivalent to an Air Force Staff Sergeant, Navy Petty Officer Second Class, Army Sergeant, and Marine Sergeant.

Treatment costs:

For family members of active duty personnel, 80 percent of the approved cost was covered after the deductible was paid. For retirees and their families, 75 percent of the approved cost was covered after the deductible was paid. The beneficiary paid any amount over the approved cost up to 15 percent of the approved cost. Treatment could be available at the MTF if space were available after TRICARE Prime patients had been served. Treatment at a MTF was free.

Provider Choice: No limitations on provider or medical facility choice.

3) TRICARE Extra – offered lower costs when beneficiaries received their care from civilian network providers.

Enrollment fees: None

Deductibles: Same as TRICARE Standard

Treatment Costs: The cost share was 5 percent less than TRICARE Standard.

Provider Choice: The choice of provider was limited to those who agreed not to charge more than an approved rate.

TRICARE medical benefits did not extend to beneficiaries 65 years or older because Medicare pays for medical costs. In October 2001 changes in TRICARE health benefits extended TRICARE medical coverage as a secondary payer to Medicare in those 65 years and older in the program known as TRICARE for Life.

TRICARE pharmacy benefits

The TRICARE Pharmacy Program provided three major points of service with differing levels of prescription co-payment (TRICARE Management Activity, 2002a). Generic substitution was required when a bioequivalent generic was available.

1) Military Treatment Facilities

   There was no co-payment for prescriptions supplied by the MTF. Up to a 90-day supply could be obtained.

2) National Mail Order Pharmacy (NMOP)

   Active duty (AD) service members could obtain up to a 90-day supply of medication with no co-pay. For any beneficiary other than active duty personnel the co-pays were $3 per prescription for generic drugs or $9 per prescription for name brand drugs for up to a 90-day supply.

3) Retail Pharmacy

a) Network Pharmacies

AD could obtain up to a 90-day supply of medication with no co-pay. For any beneficiary other than AD personnel the co-pays were $3 per prescription for generic drugs or $9 per prescription for name brand drugs for up to a 30-day supply.

b) Non-network Pharmacies

$9 or 20 percent of total drug cost (whichever is greater)

Deductible: $50/person; $100/family for E-4 rank or below

Standard: $150 person/$300 family

Prime $300 person/600 family (POS fee 50 percent)

Any DoD beneficiary, regardless of age, was eligible to receive medications from the MTF at no charge. Before April 2001 TRICARE pharmacy benefits did not extend to beneficiaries 65 years or older. Any medications obtained outside of the MTF by beneficiaries 65 years or older were at personal expense unless the person was covered by privately purchased supplemental insurance. In April 2001 changes in TRICARE pharmacy benefits extended TRICARE retail and NMOP pharmacy benefits to those 65 years and older.

TRICARE was secondary payer for any beneficiaries with other health insurance. If patients were covered by other insurance, they were required to submit the claim to their primary insurance. Any amount not covered by the primary insurer could be submitted for secondary payment by TRICARE.

The TRICARE plan covered medically necessary, legally written prescriptions for U.S. FDA-approved legend drugs, as well as insulin and diabetic supplies. TRICARE would not cover prescriptions prescribed or furnished by a member of the patient's immediate family nor would it cover the following drugs:

Drugs previously requiring a prescription, but now available OTC

Drugs used to support or maintain existing or potential drug abuse

Obesity, weight control (appetite suppressants)

Medication for transexualism or gender dysphoria

Medication for non-coital reproductive procedures

Medication related to "stop smoking" programs

Medications connected to cosmetic purposes/aging

Placebos

Vitamins and food products or substitutes

Terbutaline therapy for in-home tocolysis

All MTF pharmacies have a closed formulary system. Any drug listed on the formulary is available to military and civilian prescribing physicians. The scope of the formulary varied based upon the size and services provided by the MTF; however, each MTF was required to stock a battery of core formulary medications. This core formulary was developed and updated by medical and pharmacy representatives from the Army, Navy, and Air Force on the DoD Pharmacy and Therapeutics Committee; thus, the core formulary requirement spanned all the military branches.

The framework of the TRICARE healthcare benefit explains some of the behavior patterns of its beneficiaries in their use of the system and some of the issues that the Lead Agent and medical service contractors deal with in administering the TRICARE plan. For example, in those 65 or older, TRICARE was not an option until October 2001. Medicare, with or without a supplemental insurance plan, was the primary payer for medical services in this age group. Because Medicare did not have a drug benefit, the only option for those 65 and older to obtain their drug benefits was through the MTF. Since the drug costs for this age group could amount to substantial out-of-pocket costs, these beneficiaries would often travel long distances to use the MTF pharmacy. In contrast, the MTFs were only funded to provide medical services to beneficiaries within a 40-mile catchment area. The underfunded MTFs had no incentive to add higher priced and/or newly marketed drugs to their formularies that would mainly be used by the over 65 population. By law, any drug on the formulary had to be available to all eligible beneficiaries. When the newer, high cost drugs were not available on the MTF formulary, those under 65 in the 40-mile catchment area for which the MTF was responsible, were forced to use either the retail pharmacies or the NMOP. Thus, the regional contractors were left reimbursing for services on mainly the high cost items. Depending upon the wording of the contract, these charges could potentially be billed back to the MTF when the patient was enrolled at the MTF. On the other hand, the regional contractors had an incentive to encourage those enrolled with civilian providers to obtain prescriptions from the MTF or the NMOP. While clinic services could restrict

access to their appointments to those enrolled in TRICARE Prime, the pharmacies at the MTFs could not.

By the co-pay structure, patients were given the incentive to obtain prescriptions in the most cost-effective manner for the DoD. The MTF was the least expensive source of medications with no co-pay and up to 90-day supplies but it had the most restrictive formulary. NMOP had co-pays, but a larger formulary and still provided up to 90-days. The convenience of a local retail pharmacy came at the price of reduced days' supply and additional co-pays.

Conclusions

While there are abundant adverse drug reaction studies in the literature most have focused on adverse drug reactions that contributed to hospital admission or occurred while in the hospital. The measurement of outpatient adverse drug reactions is hindered by the inability of researchers to gain access to medical records as well as the financial costs of conducting the intensive surveillance methods undertaken in a hospital setting. Claims database research is one method of assessing adverse drug reactions that appears conducive to the outpatient setting. This appears to be especially true when applied to a managed care type setting where the majority of the recommendations for an ideal database can be achieved (van Eijk et al., 2001).

Although claims databases have been used to study adverse effects of individual drugs, there are no reports in the literature using a claims database to assess the occurrence of adverse drug reactions with a corresponding evaluation of these occurrences for associated risk factors. The ability to detect adverse drug reactions and

predict the elements that put ambulatory patients most at-risk for their occurrence is the initial step towards developing adverse drug reaction preventive measures. Despite the inherent limitations, adverse drug reaction study using claims database information appears to be one of the few promising, cost-efficient, labor-reducing methods to identify adverse drug reactions in an outpatient population.

CHAPTER 3: METHODOLOGY

This study focused on identifying adverse drug reaction risk factors and the associated expenditures in an ambulatory population using a medical and pharmacy insurance claims database. The project was divided into two major sections. Section one entailed developing methods to identify adverse drug reactions using claims data. Section two pertained to assessing six literature-identified risk factors and associated expenditures for those persons with an adverse drug reaction compared to those without an adverse drug reaction.

Definition

An adverse drug reaction (ADR) was defined as any noxious change in a patient's condition which occurred at dosages normally used in humans, and which a) required treatment, or b) indicated decrease or cessation of therapy with a drug, or c) suggested that future therapy with the drug carried an unusual risk in this patient (Koch-Weser, 1968). Medication errors, intentional or accidental overdoses, and therapeutic failures were excluded by this definition.

Data source

This study used the medical and pharmacy claims data submitted to one of the TRICARE regional contractors between 1 October 1999 and 31 October 2001 for reimbursement of medical services or pharmaceutical products. The managed care contractor for this region administered the TRICARE healthcare plan over a 16-state catchment area comprised of approximately 1.1 million eligible beneficiaries. TRICARE

Prime enrollees made up 34.2 percent (377,000) of these beneficiaries with 40,000 (10.6 percent) of these utilizing the TRICARE network (non-MTF). Approximately 73 percent of TRICARE non-Prime beneficiaries utilized the TRICARE network. The claims data contained in this database were for medical encounters obtained outside of the MTFs and for pharmaceuticals obtained from sources other than the MTFs or the NMOP. The region contained 27 military treatment facilities. Seven states had one MTF, three states had two MTFs, two states had three MTFs, and two states had four MTFs. Two states did not have a MTF (Appendix A).

The pharmacy claims database used in this study captured only the pharmacy claims submitted through retail pharmacies. Over all the regions within the continental Unites States, prescriptions filled by the retail pharmacies made up approximately 22 percent of TRICARE's total prescription volume. The remaining percentages of prescriptions were filled at the MTF or the NMOP. Region-specific breakdowns of points of service were not available to the regional contractor; however, because the size of the MTF pharmacies and their formularies are relatively small and the geographical area covered by the Central Region is greater than in other regions, it is anticipated that this region has a much higher level of retail pharmacy use than the overall TRICARE percentage. Approximately 70 percent (6,500) of the retail pharmacies in the region were TRICARE-enrolled network pharmacies.

Study subjects

Because the literature reported different adverse drug reaction experiences in children versus adults, the data set was divided into two groups: those less than 18 years

of age (child) and those 18 years of age or older (adult). Patients who were between one and 182 days old were rounded to 0.5 years of age. Patients between 183 days and 364 days old were rounded to one year of age.

Between the inclusive dates of this study, each of the TRICARE-eligible beneficiaries had the option to participate in one of three TRICARE programs: TRICARE Prime, TRICARE Extra, or TRICARE Standard. As previously described, the plans differed by enrollment requirements, deductible amounts, medical treatment and pharmacy co-payment amounts, and provider choice.

Medical and pharmacy claim files were linked by a unique patient identifier that allowed patient-level tracking. The unique identifier was also linked to a patient demographic or member file that included the patient's age and sex. Because of the structure of the TRICARE program, the region's medical service contractor did not have the traditional type of enrollment file that exists in other managed care organizations. Beneficiaries could potentially access the TRICARE network without appearing in the member file. The patient had to appear in all three files: pharmacy, medical, and member, in order to be included in the study. All patient identification numbers were uniquely encrypted by the medical service contractor prior to release of the data to the investigator. Patient birth dates were converted to years of age.

This study was reviewed by the University of Arizona Human Subjects Protection Program and approved as study number BSC B01.59 under the Social and Behavioral Sciences Human Subjects Committee on 21 December 2001 (Appendix B).

Section 1: Identifying adverse drug reaction cases in the database

There is limited adverse drug reaction information in claims data. Since this study method did not have access to medical record documentation with which to verify an adverse drug reaction, three methods were developed to identify those adverse drug reactions that would provide the strongest level of causal suspicion given the limitations of the data source.

Method One: Identification through ICD-9-CM Codes

Using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, a list of diagnostic and supplementary codes was compiled and served as trigger codes for an adverse drug reaction. These codes were divided into three categories.

In the first ICD-9-CM category were the event codes or E-codes E930 through E949 (Health Care Financing Administration, 2001). These codes identified situations in which the correct drug was properly administered in a therapeutic or prophylactic dosage and deemed to be the cause of an adverse effect, including allergic or hypersensitivity reactions. This category excluded accidental and intentional overdoses, events in which the wrong drug was given or taken in error, and accidents in drug administration.

The second ICD-9-CM category was based on a list from a previous study that attempted to identify adverse drug events in outpatients using electronic medical records and ICD-9-CM codes (Honigman, Light, Pulling, & Bates, 2001). From that list, codes 583.9 (nephropathy), and 693.1-693.9 (ingestion dermatitis) were considered nonspecific for drug causes and were excluded from this list. In addition, codes 960-977: poisoning

by drugs, medicinal and biological substances, were excluded because these codes indicated overdoses or drug errors and, therefore, did not meet the definition of an adverse drug reaction. Code 692.3 was also excluded because it was specific for contact dermatitis due to drugs and medicines in contact with the skin. This method was restricted to oral medications; therefore, this code was excluded. The ICD-9-CM codes that were retained are noted in Table 5.

The third category of ICD-9-CM codes consisted of four codes that were specific for adverse drug reactions, for example, the ICD-9-CM code for Parkinsonism due to drugs.

Table 5. ICD-9-CM codes for method one

E930-E949	Drugs, medicinal and biological substances causing adverse effects in therapeutic use
284.8[b]	Other specified aplastic anemia (due to drugs)
288.0[b]	Agranulocytosis (neutropenia: drug-induced)
292.xx[b]	Drug psychoses
332.1[b]	Secondary Parkinsonism (Parkinsonism due to drugs)
535.4[ab]	Other specified gastritis
693.0[ab]	Dermatitis due to substances taken internally: due to drugs and medicines
708.0[ab]	Allergic urticaria
995.0[a]	Other anaphylactic shock, adverse effect of correct medicine properly administered
995.2[a]	Unspecified adverse effect of drug, medicinal and biological substance

[a] Adapted from Honigman, Light et al., 2001
[b] ICD-9-CM code screened for medications listed in Appendix C

The medical claims captured by the ICD-9-CM codes within these three categories were flagged and the profiles examined for causative drug exposures within 30 days prior to the targeted ICD-9-CM code. The E-coded events required proof of an exposure to the corresponding medication in the medication class coded by the E-code.

For example, a pharmacy claim for a synthetic or semisynthetic penicillin within 30 days prior to the ICD-9-CM code E930.0 (antibiotics; penicillins) was required in order to consider the event an adverse drug reaction.

For seven of the coded conditions other than those that were E-coded, pharmaceutical science and medical reference texts were used to identify and target medications and/or classes of medications most commonly associated with the diagnoses of interest (Chisholm & Jackson, 2002; Garnett & Dukes, 1988; Klinker, Harbilas, & Johns, 2002; Lamberg, 2002; Nelson, Berchou, & LeWitt, 2002). These medications were used as a type of database screening to create an automated and objective method of identifying an adverse drug reaction. A pharmacy claim for one of the screening medications needed to occur within 30 days prior to its corresponding ICD-9-CM in order to be eligible as a potential adverse drug reaction case. The medications used for this automated screening are listed in Appendix C. Those codes that were screened for specific drug exposures are annotated in Table 5. The two remaining codes, ICD-9-CM 995.0 and 995.2, were not screened for specific drug exposures. Any drug exposure within 30 days prior to the coded encounter qualified as an adverse drug reaction for either of these two remaining codes.

To avoid counting the same reaction multiple times, a 90-day waiting period was applied to each reaction that had the same ICD-9-CM code. For instance, if ICD-9-CM 284.8 were identified on 1 January, a second claim for ICD-9-CM 284.8 for the same patient within the next 90 days would not be considered a second trigger code. In addition, the same ICD-9-CM trigger code was considered a maximum of two times for

one patient and must have occurred at least six months apart. If the same ICD-9-CM occurred more than twice in a single patient's profile, the event was considered a chronic rather than an acute episode and only the first reaction was retained for the analysis.

Method Two: Identification through targeted drugs

Method two used the medication as the trigger mechanism. Four drugs and/or classes of drugs were identified in the adverse drug reaction literature as the most common medications producing adverse drug reactions: digoxin, anticoagulants, anti-infectives, and NSAIDs. Because digoxin's adverse effects would be identified with an E-code as in method one, it was dropped from method two. The medical claims of patients with any of the oral versions of the remaining three classes of drugs in their prescription profile were flagged and screened for corresponding ICD-9-CM codes indicative of an adverse drug reaction (Table 6). The ICD-9-CM codes selected were based upon the most frequent adverse clinical manifestations reported in the outpatient adverse drug reaction studies.

In addition, claims containing drugs and/or drug combinations that indicated a strong suspicion of an adverse drug reaction were also flagged for further examination. An example of this would be a prescription for sodium polystyrene sulfonate prescribed subsequent to a potassium replacement prescription. These combinations were commonly used medication order screening mechanisms for adverse drug reactions because they were often used to counteract an adverse drug reaction (Table 7) (Honigman et al., 2001). The corresponding ICD-9-CM outcome codes of interest are also included in Table 7.

Table 6. ICD-9-CM codes targeted when combined with trigger medications

Targeted outcome when profile flagged with NSAID use	
531.xx	Gastric ulcer
532.xx	Duodenal ulcer
533.xx	Peptic ulcer
535.xx	Gastritis and duodenitis
578.xx	GI bleed
784.7	Epistaxis
787.0x	Symptoms involving digestive system; nausea / vomiting
Targeted outcome when profile flagged with warfarin use	
578.xx	Gastrointestinal hemorrhage
784.7	Epistaxis
786.3	Hemoptysis
Targeted outcome when profile flagged with anti-infective use	
008.45	Clostridium difficile
535.0x	Acute gastritis without/with mention of hemorrhage
535.4x	Other specified gastritis without/with hemorrhage
535.5x	Unspecified gastritis and gastroduodenitis without/with mention of hemorrhage
558.3	Allergic gastroenteritis and colitis
693.0	Dermatitis medicamentosa
695.1	Erythema multiforme (Stevens-Johnson syndrome)
708.0	Allergic urticaria
787.0x	Symptoms involving digestive system; nausea / vomiting
995.0	Other anaphylactic shock
995.1	Angioneurotic edema
995.2	Unspecified adverse effect of drug, medicinal and biological substance

NSAID Nonsteroidal anti-inflammatory drugs

Table 7. Medications indicating suspicion of an adverse drug reaction

Glucagon with a record of insulin use within the past 90 days ICD-9-CM: 250.8, Diabetes with other specified manifestations (diabetic hypoglycemia or hypoglycemic shock)
Oral corticosteroids and diphenhydramine[a] or hydroxyzine obtained concurrently (within 3 days) ICD-9-CM: 693.0, 695.1, 708.0, 995.0, 995.1, 995.2, (Defined in Table 6)
Sodium polystyrene sulfonate with: a) record of ACE[b] inhibitor therapy within the past 30 days b) record of potassium supplement therapy within the past 30 days c) record of potassium-sparing diuretic therapy within the past 30 days ICD-9-CM: 276.7, Hyperkalemia

[a] Over-the-counter strengths/products could not be captured in the database
[b] Angiotensin converting enzyme

Method Three: Identification through inappropriate prescribing criteria

In previous studies, expert panels established consensus criteria which identified drug use that was contraindicated in the ambulatory elderly (Beers, 1997; McLeod et al., 1997). The contraindication could be secondary to an increased potential to induce an adverse drug reaction. These drugs were considered to have either an unacceptable risk-benefit ratio, significant drug-drug interaction potential, or significant drug-disease state interaction potential (McLeod et al., 1997).

This study used a subset of the Beers' criteria (Table 8). The drug-disease state criteria from Beers' study that were reported to have a high severity level, that is, a high adverse drug reaction potential, were included in this analysis with two exceptions. According to the Beers' criteria the use of diet pills and amphetamines was contra-indicated in hypertensive patients; however, since this class of drugs was not covered by

TRICARE, this criterion could not be included. Second, the blood-clotting disorders criterion was considered too ill-defined to include.

Although the Beers' criteria were developed to apply to the elderly population, this analysis did not limit the search criteria by age for two reasons. First, prior to October 2001 the TRICARE insurance plan did not cover most patients 65 years or older, so only a small number of this targeted population would be contained in the database. Second, general precautions for the use of these drugs in patients with these particular disease states or conditions, regardless of age, was considered standard practice.

An automatic screening searched for patients with the diagnosis or condition who were prescribed the contraindicated drug within 30 days after the targeted diagnosis. Any medical claims submitted within 30 days after the diagnosis/drug match were reviewed automatically and manually for existence of indicators of worsening disease state, for example, acute asthma exacerbation or respiratory distress in those with asthma.

Table 8. Inappropriate prescribing criteria (Adapted from Beers, 1997)

Disease and Condition	Drug	Alert
Heart failure	Disopyramide	Negative inotrope. May worsen heart failure.
ICD-9-CM: 428.0 CHF, 428.1 left heart failure, 428.9 heart failure, unspecified		
COPD	β-blockers	May worsen respiratory function in COPD
	Sedatives/hypnotics	May slow respirations and increase carbon dioxide retention in persons with severe COPD
ICD-9-CM: 493.20 chronic obstructive asthma (without mention of status asthmaticus or acute exacerbation or unspecified)		
Asthma	β-blockers	May worsen respiratory function in COPD
ICD-9-CM: 493.00 extrinsic asthma, 493.10 intrinsic asthma, 493.9 asthma, unspecified (without mention of status asthmaticus or acute exacerbation or unspecified)		
Ulcers	NSAIDs	May exacerbate ulcer disease, gastritis, & GERD
ICD-9-CM: 531.4 – 531.9 gastric ulcer (chronic), 532.4 – 532.9 duodenal ulcer (chronic), 533.4 – 533.9 peptic ulcer (chronic), 534.4 – 534.9 gastrojejunal ulcer (chronic)		
PVD	β-blockers	May worsen peripheral arterial blood flow and precipitate claudication
ICD-9-CM: 443.0 Raynaud's syndrome; 443.9 peripheral vascular disease, unspecified		
BPH	Anticholinergic antihistamines	Anticholinergics may impair micturation and cause obstruction in persons with BPH
	Gastrointestinal antispasmodics	Anticholinergics may impair micturation and cause obstruction in persons with BPH
	Anticholinergic antidepressants	Anticholinergics may impair micturation and cause obstruction in persons with BPH
ICD-9-CM: 600.0 hypertrophy (benign) of prostate		
Constipation	Tricyclic antidepressants	May worsen constipation
ICD-9-CM: 564.0 constipation		
Syncope or falls	Long-acting benzodiazepines	May contribute to falls
ICD-9-CM: 780.2 syncope and collapse		
Arrhythmias	Tricyclic antidepressants	May induce arrhythmias
ICD-9-CM: 427.xx cardiac dysrhythmias		

COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure
NSAID – nonsteroidal anti-inflammatory drugs; BPH – benign prostatic hypertrophy
PVD – peripheral vascular disease

Summary of adverse drug reaction detection methods

Table 9 lists the specific drugs targeted by this study and is a compilation and expansion of the components included in Tables 5, 6, 7, and 8. Prescriptions were assigned to drug groups based on the Generic Product Identifier (GPI) number (First Databank (Medispan), 1999). The GPI is a unique 14-digit code that allows a specific product to be identified or a class of products to be identified. Classification of prescription medications within the GPI coding is hierarchical with the first two digits representing the drug group and the subsequent groups of digits narrowing the classification down to specific agents within the group.

When a drug or drug class was targeted only in conjunction with a specific ICD-9-CM code, the appropriate code is also listed in the table. Likewise, when the medications were targeted only in combinations with certain other medication classes, the corresponding medication parameters are stated in the table.

Table 10 contains the complete list of ICD-9-CM codes compiled from all three methods of adverse drug reaction identification. Like Table 9 it is a compilation and expansion upon the components included in Tables 5, 6, 7, and 8.

Table 9. Targeted medication list

Anticholinergic Antihistamines[b]

ICD-9-CM: 600.0, hypertrophy (benign) of prostate

Diphenhydramine	Hydroxyzine
Cyproheptadine	Promethazine
Tripelennamine	Dexchlorpheniramine

Tricyclic Antidepressants[b]

ICD-9-CM: 427.xx, cardiac dysrhythmias

(High Anticholinergic Side Effect*)

Amitriptyline*	Amoxapine*
Clomipramine*	Desipramine
Doxepin	Imipramine*
Nortriptyline	Protriptyline*
Trimipramine	

Anti-infectives[a]

ICD-9-CM: per Table 6

Antibiotic class	Antituberculous drug class
Antifungal class	Amebicide class
Antiviral class	

β-blockers with β_2 adrenergic-receptor blocking activity[b]

ICD-9-CM: 493.2 COPD; 493.xx, asthma

Carteolol	Nadolol
Penbutolol	Pindolol
Propranolol	Sotolol
Timolol	

β-blockers[b]

ICD-9-CM: 443.0 Raynaud's syndrome; 443.9 peripheral vascular disease

(in addition to the list above)

Acebutolol	Atenolol
Betaxolol	Bisoprolol
Metoprolol	

Benzodiazepines[b]

ICD-9-CM: 780.2, syncope and collapse

(long-acting with half life > 24 hour)

Diazepam	Quazepam
Flurazepam	

Table 9. Targeted medication list (continued)

Gastrointestinal Antispasmodics[b]

ICD-9-CM: 600.0, hypertrophy (benign) of prostate

Belladonna Alkaloids	Clidinium-Chlordiazepoxide
Dicyclomine	Hyoscyamine
Propantheline	

Glucagon[a]

ICD-9-CM: 250.8, Diabetes with other specified manifestations

Disopyramide[b]

ICD-9-CM: 428.0 CHF, 428.1 left heart failure, 428.9, heart failure, unspecified

Sedative/hypnotics[b]

ICD-9-CM: 493.20 COPD

Chloral Hydrate	Estazolam
Flurazepam	Quazepam
Temazepam	Triazolam
Zolpidem	

Nonsteroidal Anti-inflammatory Drugs[ab]

ICD-9-CM: 531.xx gastric ulcer; 532.xx duodenal ulcer; 533.xx peptic ulcer; 534.xx gastrojejunal ulcer

Choline magnesium trisalicylate	Meclofenamate sodium
Celecoxib	Mefenamic acid
Diclofenac	Nabumetone
Diflunisal	Naproxen
Etodolac	Naproxen sodium
Fenoprofen	Oxaprozin
Ibuprofen	Piroxicam
Indomethacin	Rofecoxib
Ketoprofen	Salsalate
Ketorolac	Sulindac
Magnesium salicylate	Tolmetin sodium

Oral corticosteroids when prescribed with antihistamines[a]

Cortisone	Prednisone
Hydrocortisone	Prednisolone
Dexamethasone	Triamcinolone
Betamethasone	Methylprednisolone

Table 9. Targeted medication list (continued)

Warfarin[ab]

ICD-9-CM 784.7 epistaxis; 786.3, hemoptysis; 578.xx GI bleed;

Sodium polystyrene sulfonate[a] when prescribed with:

Angiotensin converting enzyme inhibitors

Benazapril	Captopril
Enalapril	Fosinopril
Lisinopril	Moexipril
Quinapril	Ramipril
Trandolapril	

Potassium-sparing diuretics

Amiloride	Spironolactone
Triamterene	

Potassium replacement products

Potassium chloride	Potassium gluconate
Potassium bicarbonate	

[a] Used in adverse drug reaction identification method two

[b] Used in adverse drug reaction identification method three

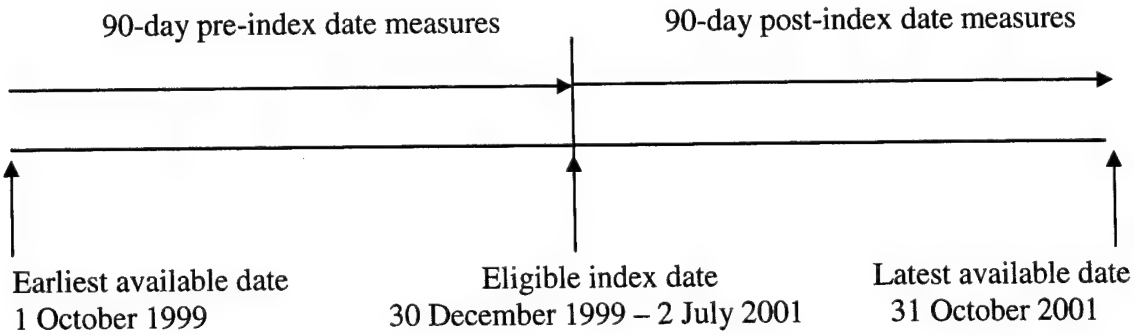
Table 10. ICD-9-CM adverse drug reaction trigger codes

E930-E949	Drugs, medicinal and biological substances causing adverse effects in therapeutic use
008.45	Clostridium difficile
250.8	Diabetes with other specified manifestations
276.7	Hyperpotassemia
284.8	Other specified aplastic anemia (due to drugs)
288.0	Agranulocytosis (neutropenia: drug-induced)
292.xx	Drug psychoses
332.1	Secondary Parkinsonism (Parkinsonism due to drugs)
427.xx	Cardiac dysrhythmias
428.0	Congestive heart failure
428.1	Left heart failure
428.9	Heart failure, unspecified
443.0	Raynaud's syndrome
443.9	Peripheral vascular disease, unspecified
493.xx	Asthma and chronic obstructive asthma
531.xx,	Gastric ulcer
532.xx	Duodenal ulcer
533.xx	Peptic ulcer
535.xx	Gastritis and duodenitis
558.3	Allergic gastroenteritis and colitis
564.0	Constipation
578.xx	Gastrointestinal hemorrhage
600.0	Hypertrophy (benign) of prostate
693.0	Dermatitis due to substances taken internally: due to drugs and medicines
695.1	Erythema multiforme
708.0	Allergic urticaria
780.2	Syncope and collapse
784.7	Epistaxis
786.3	Hemoptysis
787.0x	Symptoms involving digestive system
995.0	Other anaphylactic shock, adverse effect of correct medicine properly administered
995.1	Angioneurotic edema
995.2	Unspecified adverse effect of drug, medicinal and biological substance

Research Design

This study is a retrospective claims database study. The date of the suspected adverse drug reaction was considered the index date. Reimbursed medical expenditures for the 90 days prior to the index date were used as a pre-event proxy measure of expenditures. Reimbursed medical expenditures for the 90 days after the index date were used as the post-event proxy measure of expenditures (Figure 2). The number of unique medications identified within the 90 days prior to the index date was used as the proxy for the number of medications. The number of pharmacies submitting claims within the 90 days prior to the index date was used as the proxy for the number of pharmacies. The subject's chronic disease score (Von Korff, Wagner, & Saunders, 1992) was calculated based upon the six month period encompassed by the 90-day pre and post index date claims.

Figure 2. Study timeline example



Section 2: Building and assessing the mathematical models

The mathematical modeling for this study was centered on two major elements. The first was the construction of a model that best fit the data for adverse drug reaction

risk factor modeling. The second was assessing the resource use and associated expenditures.

Dependent variables for risk factor modeling

The dependent variable or outcome variable for the risk factor analysis was the occurrence of an adverse drug reaction measured by the three different identification methods.

Independent variables for risk factor modeling

Independent variables consisted of factors believed to have an association with the occurrence of an adverse drug reaction. These were:

- age (continuous variable in years)
- sex (dichotomous; 0 = male, 1 = female)
- number of pharmacies (continuous variable)
- chronic disease score (continuous variable)
- number of prescribers (continuous variable)
- number of prescription medications (continuous variable)

The chronic disease score (CDS) is a summary measure of co-morbidity that was constructed by an expert panel of physicians, pharmacists, epidemiologists, and health services researchers (Von Korff et al., 1992). The CDS used a method of scoring automated pharmacy data to provide a stable measure of chronic disease status and served as a proxy for co-morbidity in the analysis. The CDS weighted its score based upon the occurrence of any use of a preset list of medication classes used in the treatment

in any of 17 different chronic conditions. Diseases that were potentially life-threatening or progressive received higher scores than a more stable or benign disease. The CDS scoring rules also increased with the number of different chronic diseases and the complexity of the regimen. The scoring rules required that medications target the disease rather than the symptoms; therefore, medications like analgesics, sedative-hypnotics, and so forth did not contribute to the disease score. Von Korff and colleagues concluded that after controlling for health care utilization, the CDS was associated with physician-rated disease severity and patient-rated health status and that those with a CDS of 7 or greater were at greater risk of hospitalization and death.

Dependent variables for assessing associated expenditures

The dependent variable for assessing adverse drug reaction-associated expenditures was the post-index date direct pharmacy and medical expenditures. These expenditures were defined as the sum of the medical and pharmacy claims reimbursed by TRICARE within 90 days after the index date.

Independent variables for assessing associated expenditures

The independent variables for assessing associated expenditures included the same independent variables as those in the risk factor model in addition to the pre-index date expenditures. The pre-index date total expenditures were defined as the sum of the medical and pharmacy claims reimbursed within 90 days prior to the index date.

The pre-index date medical expenditures were collapsed into four place of service categories: inpatient hospital, emergency department, physician's office, and other medical sites.

Analysis

A chi-square test was used to assess for differences between cases and controls when the variable was categorical (gender). Unpaired t-tests were used to assess for differences between cases and controls for the continuous variables: age, number of medications, number of pharmacies, CDS, and expenditures.

Logistic regression techniques were used to test for associations between the risk factors of age, gender, number of pharmacies, number of medications, and CDS and the risk of an adverse drug reaction. Multiple linear regression techniques were used to assess for an association between the risk factors and post-index date expenditures. All statistical tests were done using the statistical software package Intercooled Stata 6.0, Statistics/Data Analysis, Stata Corporation (College Station, TX).

Logistic regression

Multiple logistic regression analysis was used to incorporate the independent variables into a model that provided the best predictive model for the occurrence of a binary outcome y with a probability of success = p (Equation 1) (Rosner, 2000).

$$\text{logit (p)} = \ln\left[\frac{p}{1-p}\right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k \qquad \text{Equation 1}$$

Where $x_1, x_2 \ldots x_k$ = first, second, through kth independent variable

α = intercept

β_1 = slope corresponding to the first independent variable

β_2 = slope corresponding to the second independent variable

β_k = slope corresponding to the *k*th independent variable

The logistic-regression model's independent variables could be continuous or categorical variables. The logit function is used to find the odds of being in one of the categories of the dependent variable given a combination of scores on the independent variable. It is evaluated by assessing the natural log likelihood for each model which is then compared by calculating the difference between the log-likelihoods (Tabachnick & Fidell, 2001a).

The independent variables for this analysis were the literature-based risk factors for the dependent variable (adverse drug reaction). Replacing the *x* terms with the risk factors yields Equation 2.

$$\ln\left[\frac{p}{1-p}\right] = \alpha + \beta_1(Age) + \beta_2(Sex) + \beta_3(Pharm) + \beta_4(Meds) + \beta_5(CDS) + \beta_6(MD)$$

Equation 2

The independent variables on the patient level included:

A*ge* (continuous variable in years)

Sex (dichotomous; 0 = male, 1 = female

Pharm (number of pharmacies; continuous variable)

Meds (number of prescription medications; continuous variable)

CDS (chronic disease score; continuous variable)

MD (number of prescribers; continuous variable)

The β-coefficients are the measure of association between each independent variable and a linear change in the outcome (log-odds) after adjusting for the influence of each of the other variables. A positive β-coefficient corresponded to an increased

likelihood of the outcome while a negative β-coefficient corresponded to a decreased likelihood.

This model was used for each of the subsets of the population that were found by the three adverse drug reaction identification methods.

Interaction terms

To assess whether there was a difference in the level of association between the risk factor and the dependent variable due to the influence of a third variable, interaction terms were introduced into the model. Interaction terms are multiplicative terms between the risk factor and a third variable. Potential interactions that were assessed were based upon the literature review. Anticipated interaction terms included age*number of medications; age*CDS; CDS*number of medications; and sex*number of medications. With the interaction term ($x_1 * x_2$), the generic logistic regression model becomes as shown in Equation 3.

$$\text{logit (p)} = \ln\left[\frac{p}{1-p}\right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_k x_1 * x_2 \qquad \text{Equation 3}$$

Predictive ability of the model

The Hosmer-Lemeshow test was used to assess the predictive ability of the model, that is, the goodness-of-fit (Hosmer & Lemeshow, 1989). This test uses a grouping strategy to obtain a goodness-of-fit statistic that is obtained by calculating the Pearson chi-square statistic from a 2 x g table of observed and estimated expected frequencies and provides a single easily interpretable value to assess fit. While grouping

can be by either percentiles or fixed cutpoints, Hosmer and Lemeshow prefer the use of percentiles because they have a better adherence to the χ^2(g-2) distribution, especially when the estimated probabilities are small. The appropriateness of the p-value of this test will depend on the estimated expected frequencies being large enough (usually > 5).

There are several disadvantages of the Hosmer-Lemeshow test. First, it does not reject often enough. Second, it has a low power to detect specific types of lack of fit such as nonlinearity in the independent variables. Third, if too few groups are used to calculate the test statistic, it will almost always indicate that the model fits.

Multivariate linear regression

The associated expenditures were assessed using ordinary least squares (OLS) regression. OLS regression allows for a continuous dependent variable while still allowing for categorical or continuous independent variables. Regression methods can be used on data in which the independent variables are correlated with each other and with the dependent variable in varying degrees, but the regression is best when each independent variable is strongly correlated with the dependent variable but uncorrelated with the other independent variables (Tabachnick & Fidell, 2001b). The standard model for OLS is shown in Equation 4.

$$DV = \alpha + \beta_1 x_1 + \beta_2 x_2 + ...\beta_k x_k \qquad \text{Equation 4}$$

DV is the predicted value on the dependent variable

α is the Y intercept value (value of Y when all the X values are zero)

$\beta_1, \beta_2, \ldots \beta_k$ are the coefficients assigned to each independent variable

$x_1, x_2, \ldots x_k$ represent the independent variables

Replacing the generic variables in Equation 4 with the study-specific variables produces Equation 5.

$$DV = \alpha + \beta(age) + \beta(sex) + \beta(Pharm) + \beta(Meds) + \beta(CDS) + \beta(MD) + \beta(preCost)$$

Equation 5

In this equation, the dependent variable is the post-index date expenditures. The independent variables were the same as those in the logistic regression model with the addition of the pre-index date expenditures (pre-Cost) variable. This variable was the pre-index date proxy measure for total direct medical and pharmacy expenditures within 90 days of the index event. A dummy variable for adverse drug reaction (0 = no adverse drug reaction, 1 = adverse drug reaction) was also included in the model.

OLS requires the variables meet several assumptions (Tabachnick & Fidell, 2001b). Diagnostic analyses were used to determine whether these assumptions were met. The diagnostic of most concern with this study is that OLS regression requires that the dependent variable have a normal distribution. The distributions of medical expenditures tend to be skewed. This skewed distribution can be rectified by deleting, rescoring, or transforming the data. Using the natural log of expenditures (transformation) can produce a normally distributed dependent variable; however, interpretation of the results becomes more complex. The variable distributions were examined for normality and transformed where appropriate.

Sample size

For regression analyses, it is not possible to calculate ahead of time what a reasonable value for a regression coefficient might be so, it was recommended that the "number of data be considerably more than the number of variables" with the rule of thumb requiring a sample size of 10 times the number of variables for logistic models and 5 to 10 times the number of variables in multiple regression models (Norman & Streiner, 2000). A computer program that based its approximate sample size calculations on a method developed by Hsieh, estimated a sample size of 401 was needed at an alpha level of 0.05 and a power of 80 percent (Methodologist's Toolchest, 2000).

For multiple linear regression, recommendations were for a cases-to-independent variable ratio of $N \geq 50 + 8m$ (where m is the number of independent variables) for testing the multiple correlation and $N \geq 104 + m$ for testing individual predictors (Tabachnick & Fidell, 2001a). Since there are eight predictors in the multiple regression model, this would require 50 + (8*8) = 114 cases to test regression and 104 + 8 = 112 cases for testing individual predictors. Tabachnick's rule of thumb assumes a medium-size relationship between the independent and dependent variables, alpha of 0.05, and beta of 0.2.

Assumptions

The following are assumptions of this research.

The download of claims from the regional contractor occurred between 1 March and 18 April 2002. The 4-month time lag between the study's inclusive dates and the

download was assumed to be sufficient to allow all relevant claims to have been submitted and processed.

ICD-9-CM classification was assumed to be accurate, complete, and consistent between facilities.

If one claim appeared within the year, it was assumed the beneficiary was TRICARE eligible for care that entire year.

It was assumed that the co-pay structure was not unduly influencing treatment options, for example, physicians were neither unwittingly prescribing nor patients preferentially requesting a medication with a higher adverse reaction profile over a medication with a lower adverse reaction profile merely because of a differential in co-payments.

Formulary limitations by the health care plan did not influence the occurrence and/or documentation of an adverse drug reaction.

Changes to the TRICARE healthcare plan in April and October 2001 were considered to have inconsequential influence on the study.

Consistent with this study's definition of an adverse drug reaction, an assumption was made that all medications occurring in the database were used in normal doses.

Limitations

Even though the recent changes in the TRICARE healthcare program were not considered influential to this study, the structure of the TRICARE healthcare program was one of the study's biggest limitations. The TRICARE plan did not restrict points of service; therefore, encounter and medication exposure information were missing for

services obtained through the NMOP or the MTF. The lack of drug exposure information could have resulted in misclassification. Since proof of drug exposure was required to identify an adverse drug reaction, the missing exposure or drug data could have resulted in failure to classify an adverse drug reaction when it should have and an underestimation of the frequency of an adverse drug reaction. Missing medical claims could have resulted in the inability to identify the outcome or adverse drug reaction and an underestimation of the frequency of an adverse drug reaction.

A clear map relating old codes to new ones, could not be assessed within the claims database. Tracking of an individual who changed family member status was not possible, for example, if an 18 year old dependent child joined the military, he or she would be covered under TRICARE prime with their coverage changing from their parent's code to their own code. The same person could potentially appear in the database under two codes.

ICD-9-CM coding is subjective. Under-reporting of adverse drug reactions can influence the type and quantity of adverse reactions captured in the study (Whipple, Ausman, & Quebbeman, 1992). Likewise, the appearance of a code does not guarantee that the reported condition was present (McCarthy et al., 2000). Coding schemes for the same conditions can also vary between facilities (Lloyd & Rissing, 1985). Multiple adverse drug reaction identification methods were used in this study to try to attenuate the influence of coding problems.

While the CDS was used in this study as a proxy for co-morbidities, an important limitation must be noted in its application to this database. The CDS uses medication use

as a proxy measure for the presence of a chronic disease. The plans in which the CDS were developed estimated that over 90 percent of prescriptions were filled within the plan's pharmacies; therefore, they were able to capture the majority of the prescriptions used by their beneficiaries (Von Korff et al., 1992). While the TRICARE healthcare program provides a pharmacy benefit to all beneficiaries, the region from which these data were drawn estimated the prescription volume captured in the data set to be much lower than this.

Due to the uniqueness of the TRICARE health program, the results of this study should not be extrapolated to other managed care organizations. This study may provide beneficial information to other TRICARE regions since they operate under similar medical service contracts.

While bias and confounding issues were discussed previously, the major threat to the internal validity of database research is a selection-maturation interaction. For example, as patients get sicker or develop additional disease states, physicians tend to prescribe more drugs. An increased medication exposure naturally suggests an increased opportunity for an adverse drug reaction. Two of the reasons given for the lack of documentation of adverse drug reactions were the uncertainty about whether the drug caused the reaction and a low level of suspicion (Schumock et al., 1991). The patient's severity of illness and quantity of medications may unduly influence the physician's suspicion and level of certainty of an adverse drug reaction and thereby effect the documentation of an adverse drug reaction. The failure to assign a patient to the adverse drug reaction group because of the lack of documentation may have affected the ability to

assess an association of co-morbidities and polypharmacy as adverse drug reaction risk factors.

The methods used to target patients for further claims' review may have inadvertently selected out subsets of the population that were preferentially prescribed medications because of disease states that predominantly occurred in different age groups or sexes.

CHAPTER 4: RESULTS

Study Population

There were 787,549 unique patients in the combined member, medical, and pharmacy files. Only 214,830 patients appeared in all three files and were eligible for initial inclusion in the study. The requirement for every patient to have a prescription medication within 30 days prior to the index date further reduced the sample to 120,028 patients. Ages in this group ranged from 0.5 to 97 years. The number of medication claims ranged from 1 to 28. The number of pharmacies used ranged from 1 to 13. The value of the chronic disease score ranged from 0 to 20.

Adverse drug reaction case identification

Method one, which targeted specific ICD-9-CM codes, identified 1,649 adverse drug reactions. Comparatively, targeting specific drugs with method two identified the most reactions with 3,779. Applying the inappropriate prescribing criteria in method three identified the least number of reactions with 60 (Table 11). The combined total was 5,488 reactions captured in 4,287 patients. An additional 115,741 patients met the inclusion criteria for the control group, yielding a total sample size of 120,028 patients. The combined method risk factor analysis retained only the initial index date reaction for those with multiple reactions. Subsequent index dates, whether captured by the same method or from a different method, were removed prior to the analysis. This resulted in removal of 1201 multiple reactions within 998 patients. Further comparison of the detection methods and responses to the thesis questions will be discussed in Chapter 5.

Table 11. Adverse drug reactions by identification method

	All ADRs	ADRs by unique patient[a]
Method 1 (Targeted ICD-9-CM codes)		
Event codes	17	14
Previous study codes	1111	765
Drug specific codes	521	428
Total	1,649	1,207
Method 2 (Targeted specific drugs)		
Anti-infectives	2,586	2,091
Warfarin	64	52
Nonsteroidal anti-inflammatory drugs	1,056	829
Glucagon with insulin	9	9
Corticosteroids with antihistamines	62	47
SPS with ACEI	1	1
SPS with potassium supplements	0	0
SPS with potassium sparing diuretics	1	0
Total	3,779	3,029
Method 3 (Targeted inappropriate prescribing)		
Heart failure with disopyramide	1	1
COPD with beta-blockers	1	1
COPD with sedative/hypnotics	6	6
Asthma with beta-blockers	5	5
Ulcers with NSAIDs	0	0
PVD with beta-blockers	11	10
BPH with anticholinergic antidepressants	1	0
BPH with antihistamines	2	2
Constipation with TCAs	21	17
Syncope/falls with benzodiazepines	0	0
Arrhythmias with TCAs	12	9
Total	60	51
Combined total	5,488	4,287

[a] Only the initial index date reaction was included in the analysis when a patient had multiple reactions

SPS sodium polystyrene sulfonate; ACEI angiotensin converting enzyme inhibitor
COPD chronic obstructive pulmonary disease;
NSAID nonsteroidal anti-inflammatory drugs; PVD peripheral vascular disease
BPH benign prostatic hypertrophy; TCA tricyclic antidepressants

Combined methods: Demographic, utilization, and CDS comparisons

Although similar demographic and regression tables were created for each of the individual methods, only the combined methods group information is presented in this results section. Appendix D, E, and F contain the individual demographic and regression model information for methods one, two, and three, respectively. Because method three yielded such a small sample size, only demographic information was compiled. Regression models were not built individually for method three. The regression models for method one and two yielded similar results to the combined models. The demographics of the combined groups are detailed in Table 12.

Cases were significantly older ($p < 0.001$) as compared to controls and predominantly female ($p < 0.001$). Cases also had a higher mean number of medications, accessed a greater mean number of pharmacies, and had a higher mean chronic disease score than controls (Table 12).

When stratified into adult and child age groups, gender was no longer significantly different between cases and controls in the group under 18 years old ($p = 0.743$). All other risk factor variables remained significantly different between cases and controls after age stratification ($p < 0.001$).

Table 12. Distribution demographic, utilization, and chronic disease score

Demographics	ADR Cases n = 4,287	Comparison Group n = 11,5741	p-value[a]
< 18 years old (percent)	703 (16.4)	26,749 (23.1)	
≥ 18 years old (percent)	3,584 (83.6)	88,992 (76.9)	<0.001
Males (percent)	1,375 (32.1)	45,998 (39.7)	
Females (percent)	2,912 (67.9)	69,743 (60.3)	<0.001
1) Age < 18 years old			
Males (percent)	426 (60.6)	16,045 (60.0)	
Females (percent)	277 (39.4)	10,704 (40.0)	0.743
2) Age ≥ 18 years old			
Males (percent)	949 (26.5)	29,953 (33.7)	
Females (percent)	2,635 (73.5)	59,039 (66.3)	<0.001
	Mean (standard deviation)		
Age	42.6 (20.4)	37.8 (20.6)	<0.001
< 18 years old	6.8 (5.5)	8.6 (5.4)	<0.001
≥ 18 years old	49.6 (13.9)	46.6 (14.5)	<0.001
Number of medications	5.3 (4.0)	2.5 (2.1)	<0.001
< 18 years old	3.0 (2.5)	1.9 (1.2)	<0.001
≥ 18 years old	5.7 (4.1)	2.7 (2.3)	<0.001
Number of pharmacies	1.3 (0.6)	1.1 (0.3)	<0.001
< 18 years old	1.2 (0.5)	1.1 (0.3)	<0.001
≥ 18 years old	1.3 (0.6)	1.1 (0.4)	<0.001
Chronic disease score	2.9 (3.2)	1.3 (2.0)	<0.001
< 18 years old	1.3 (2.1)	0.7 (1.4)	<0.001
≥ 18 years old	3.2 (3.3)	1.5 (2.1)	<0.001

[a] t-test for continuous variables; chi-square for categorical variables
N = 120,028

For the 120,028 patients in the sample, the per patient frequency rate for an adverse drug reaction over the two year period was 3.57 percent. Among the 27,452 children the rate was 2.6 percent. Among the 92,576 adults the rate was 3.9 percent (Table 13).

At least 214,830 patients were exposed to one drug over the two-year period. If these patients are considered the population at risk, then the two-year incidence rate was 1.99 percent. The two-year prevalence rate, defined as the number of new cases (5,488) divided by the total population (787,549 patients in the data set), was 0.70 percent.

Table 13: Frequency of ADRs by ages

	ADRs	No ADR	Total	Frequency (percent)
Children (years)				
< 5	334	8,238	8,572	3.90
5 – 10	162	7,730	7,892	2.05
11 – 17	207	10,781	10,988	1.88
Total	703	26,749	27,452	2.56
Adults (years)				
18 - 24	318	10,262	10,580	3.01
25 - 34	270	10,304	10,574	2.55
35 - 44	483	14,832	15,315	3.15
45 – 54	857	21,042	21,899	3.91
55 – 64	1,476	28,376	29,852	4.94
≥ 65	180	4,176	4,356	4.13
Total	3,584	88,992	92,576	3.87

The mean number of medications and the mean CDS were calculated across these same age categories and showed an increase in the mean values as age increased (Table 14).

Table 14. Distribution of the number of medications and chronic disease score by age

Age Group (years)	Number of Meds ADR Cases Mean (SD)	Number of Meds Controls Mean (SD)	CDS[a] ADR Cases Mean (SD)	CDS[a] Controls Mean (SD)
Children				
< 5	2.6 (1.9)	1.9 (1.2)	1.1 (1.9)	0.8 (1.5)
5 - 10	2.7 (2.1)	1.8 (1.2)	1.4 (2.1)	0.7 (1.4)
11 - 17	3.8 (3.2)	1.9 (1.3)	1.6 (2.4)	0.7 (1.3)
Overall	3.0 (2.5)	1.9 (1.2)	1.3 (2.1)	0.7 (1.4)
Adults				
18 - 24	3.8 (3.0)	2.0 (1.4)	1.4 (2.2)	0.6 (1.2)
25 - 34	4.8 (3.7)	2.1 (1.6)	1.9 (2.4)	0.6 (1.3)
35 - 44	5.5 (3.9)	2.4 (1.9)	2.6 (2.9)	1.0 (1.6)
45 – 54	6.0 (4.4)	2.9 (2.4)	3.3 (3.3)	1.5 (2.1)
55 – 64	6.1 (4.1)	3.2 (2.6)	3.8 (3.5)	2.1 (2.5)
≥ 65	5.9 (3.7)	3.4 (2.8)	3.7 (3.5)	2.5 (2.7)
Overall	5.7 (4.1)	2.7 (2.3)	3.2 (3.3)	1.5 (2.1)

[a] Chronic disease score

Combined methods: Characteristics of medical and pharmacy expenditures

Expenditures were defined as the actual amount reimbursed on the claim by the healthcare insurer. Expenditures were allocated by place of service code to one of five groups: pharmacy, office visit, inpatient hospital, emergency visit, and other medical. A complete list of services included within the "other medical" category and the number of claim items for each medical claim category in the complete data set are detailed in Appendix G.

Table 15 and 16 contain comparisons of expenditures between cases and controls in the 90-day pre-index and 90-day post-index date periods. Cases had significantly

greater mean pharmacy, office visit, emergency visit, inpatient, and other medical expenditures than controls. This association remained after stratification into adult and child groups.

Table 15. Comparison of claims paid 90 days prior to index date

Service Location	ADR Cases n = 4,287	Cases	Controls n = 115,741	Controls	p-value[a]
< 18 years (%)	703 (16.4)		26,749 (23.1)		
≥ 18 years (%)	3,584 (83.6)		88,992 (76.9)		< 0.001
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$380.39 (679.66)	$181.00	$152.42 (362.90)	$67.00	<0.001
< 18 years	$149.03 (566.75)	$47.00	$90.36 (447.23)	$40.00	0.007
≥ 18 years	$425.77 (690.71)	$228.00	$171.07 (331.15)	$79.00	<0.001
Office visit	$491.77 (1953.89)	$99.00	$133.80 (481.05)	$43.00	<0.001
< 18 years	$225.45 (946.11)	$83.00	$102.17 (206.67)	$46.00	0.001
≥ 18 years	$544.01 (2091.57)	$102.00	$143.31 (536.42)	$42.00	<0.001
Emergency	$149.20 (370.12)	$0.00	$68.11 (243.97)	$0.00	<0.001
< 18 years	$101.46 (338.36)	$0.00	$49.38 (170.61)	$0.00	<0.001
≥ 18 years	$158.56 (375.37)	$9.00	$73.74 (261.77)	$0.00	<0.001
Inpatient	$250.81 (1089.59)	$0.00	$99.48 (628.96)	$0.00	<0.001
< 18 years	$163.96 (832.81)	$0.00	$67.33 (701.67)	$0.00	0.002
≥ 18 years	$267.85 (1132.46)	$0.00	$109.15 (605.06)	$0.00	<0.001
Other medical	$114.61 (862.92)	$0.00	$35.01 (937.32)	$0.00	<0.001
< 18 years	$125.57 (939.01)	$0.00	$46.35 (1821.24)	$0.00	0.033
≥ 18 years	$112.46 (847.32)	$0.00	$31.60 (381.62)	$0.00	<0.001
Total claims	$1386.78 (2974.52)	$482.00	$488.82 (1456.99)	$197.00	<0.001
< 18 years	$765.47 (2296.22)	$212.00	$355.59 (2180.28)	$140.00	<0.001
≥ 18 years	$1508.66 (3075.72)	$571.50	$528.87 (1151.15)	$220.00	<0.001

[a] t-test

Table 16. Comparison of claims paid 90 days after index date

Service Locations	ADR Cases n = 4,287	Cases	Controls n = 115,741	Controls	p-value[a]
< 18 years (%)	703 (16.4)		26,749 (23.1)		
≥ 18 years (%)	3,584 (83.6)		88,992 (76.9)		< 0.001
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$433.61 (856.67)	$186.00	$148.18 (320.84)	$50.00	<0.001
< 18 years	$128.00 (335.03)	$31.00	$76.34 (214.89)	$15.00	<0.001
≥ 18 years	$493.56 (913.22)	$239.50	$169.77 (343.48)	$64.00	<0.001
Office visits	$675.28 (2552.24)	$122.00	$149.68 (500.89)	$60.00	<0.001
< 18 years	$309.25 (1713.22)	$97.00	$113.64 (213.96)	$58.00	0.003
≥ 18 years	$747.08 (2680.57)	$129.50	$160.52 (558.60)	$60.00	<0.001
Emergency visits	$175.27 (358.27)	$47.00	$73.49 (241.23)	$0.00	<0.001
< 18 years	$122.79 (327.15)	$30.00	$49.95 (162.73)	$0.00	<0.001
≥ 18 years	$185.56 (363.22)	$51.00	$80.57 (259.82)	$0.00	<0.001
Inpatient	$262.54 (1037.00)	$0.00	$65.90 (438.40)	$0.00	<0.001
< 18 years	$230.14 (1565.89)	$0.00	$21.07 (258.67)	$0.00	<0.001
≥ 18 years	$268.89 (897.61)	$0.00	$79.37 (478.60)	$0.00	<0.001
Other medical	$149.35 (1250.17)	$0.00	$28.88 (1043.20)	$0.00	<0.001
< 18 years	$199.64 (1526.67)	$0.00	$44.78 (2088.52)	$0.00	0.009
≥ 18 years	$139.49 (1188.41)	$0.00	$24.09 (322.81)	$0.00	<0.001
Total claims	$1696.05 (3635.54)	$641.00	$466.14 (1377.00)	$210.00	<0.001
< 18 years	$989.83 (3553.53)	$253.00	$305.78 (2174.50)	$136.00	<0.001
≥ 18 years	$1834.58 (3635.83)	$748.50	$514.34 (1017.25)	$241.00	<0.001

[a] t-test

Combined methods: Risk factor analysis

The first six hypotheses were to assess the affect of age, gender, number of medications, number of co-morbidities, number of physicians, and number of pharmacies on the risk of an adverse drug reaction. Because the physician field was not populated in the raw data set, hypothesis five, assessing the association between number of physicians and the risk of an adverse drug reaction, could not be tested.

The correlation matrix (Table 17) raised concerns that the higher correlation ($\cong 0.60$) between the number of medications variable and the CDS variable could be influencing the results. Norman and Streiner (2000), recommended correlations be no greater than 0.30. Therefore, the models were initially calculated with both terms in the model and then recalculated using only the number of medications variable or the CDS variable to assess for their association to the outcome.

Table 17. Correlation matrix of independent variables

	Age	Gender	Medications	Pharmacies	CDS[a]
Age	1.000				
Gender	0.118	1.000			
Medications	0.255	0.097	1.000		
Pharmacies	0.001	0.023	0.247	1.000	
CDS[a]	0.294	-0.023	0.593	0.096	1.000

[a] Chronic disease score

Age

Hypothesis 1: There is no association between age and having an adverse drug reaction.

Adverse drug reactions were detected with increasing frequency in the adult group in each decade after age 25. In children the frequency rate decreased steadily across increasing age strata (Table 13).

After controlling for the other risk factor variables, age was not significantly associated with an adverse drug reaction in the combined group ($p = 0.114$) (Table 18 – Full Model); however, when the combined group was stratified into those 18 years and older (adult) and those less than 18 years (child), age was significantly associated with an adverse drug reaction in children ($p < 0.001$) but remained nonsignificant in the adults ($p = 0.169$) (Table 19).

Interaction terms were added to the models because the increase in number of medications and the increase in the value of the CDS with the increase in age appeared to increase at different rates between cases and controls (Table 14). After interaction terms were added to the models, age was significant in adults and children ($p < 0.001$) but in different directions (Table 20). With children, an increase in age was negatively associated with an adverse drug reaction; whereas, an increase in age was positively associated with an adverse drug reaction in the adults, as one would expect.

Hypothesis one was rejected for both the adult and children models. After controlling for the other risk factors, an increase in age was associated with a greater risk of an adverse drug reaction in the adult cohort; whereas, a decrease in age was associated with an increased risk of an adverse drug reaction in the child cohort.

Gender

Hypothesis 2: There is no association between gender and having an adverse drug reaction.

After controlling for the other risk factor variables, gender was significantly associated with an adverse drug reaction in the combined group ($p < 0.001$) (Table 18);

however, when examined by age groups, gender was not significantly associated with an adverse drug reaction in the child cohort ($p = 0.934$) (Table 19).

After interaction terms were added to the models, females continued to show a greater risk of an adverse drug reaction in the adult group ($p < 0.001$), but gender was not significantly associated with an adverse drug reaction in the child group ($p = 0.875$) (Table 20).

Hypothesis two was rejected in the adult model. After controlling for the other risk factors, females had a greater risk of an adverse drug reaction than males in this population. Hypothesis two was not rejected in the child group. After controlling for the other risk factors, gender appeared to have no association with an adverse drug reaction in the children in this sample.

Number of medications

Hypothesis 3: There is no association between the number of medications the patient takes and having an adverse drug reaction.

After controlling for the other risk factor variables, number of medications was significantly associated with an adverse drug reaction in the combined group ($p < 0.001$) (Table 18). This association remained significant upon stratification into the adult and child groups ($p < 0.001$) (Table 19) and with the addition of interaction terms to the model (Table 20).

Hypothesis three was rejected. After controlling for the other risk factors, the risk of an adverse drug reaction increased with an increase in the number of prescription medications in this sample.

Number of co-morbidities

Hypothesis 4: There is no association between the number of co-morbidities the patient has and having an adverse drug reaction.

After controlling for the other risk factor variables, the CDS was significant in the combined group ($p < 0.001$) (Table 18). Upon stratification into the adult and child groups, CDS remained significantly associated with an adverse drug reaction in the adults ($p < 0.001$) but not in the child group ($p = 0.926$) (Table 19).

When the number of medications variable was pulled from the model instead of the CDS to account for the correlation between the variables, the CDS remained significant in both age groups ($p < 0.001$) prior to addition of interaction terms. Similarly to the number of medications variable, the increase in the value of the CDS appeared to be increasing with age at different rates between cases and controls (Table 14); therefore, interaction terms were added to the model. An interaction between CDS and gender was not significant. Age and CDS remained significantly associated with an adverse drug reaction after adjusting for the interaction term between CDS and age (Table 21).

Hypothesis four was rejected. After adjusting for the other risk factors and the interaction between age and CDS, the risk of an adverse drug reaction increased with an increase in the chronic disease score.

Number of pharmacies

Hypothesis 6: There is no association between the number of pharmacies the patient uses and having an adverse drug reaction.

After controlling for the other risk factor variables, the number of pharmacies was significant in the combined group ($p < 0.001$) (Table 18). This significance remained in the adult group ($p = <0.001$), but was nonsignificant in the child model ($p = 0.270$) (Table 19).

Hypothesis six was rejected in the adult group, but failed to be rejected in the child group. After controlling for the other risk factors in this sample, the risk of an adverse drug reaction increased with an increase in the number of pharmacies used by the adults.

Summary of combined methods: Full model risk factor analysis

In the child model, age, number of medications, and the age*medication interaction term were statistically significant predictors of an adverse drug reaction. In the adult model, all the variables were statistically significant predictors of an adverse drug reaction.

The interaction between age and number of medications was significant and retained in the adult and child models ($p < 0.001$ and 0.007, respectively). The interaction between gender and number of medications was only significant and retained in the adult model ($p = 0.001$).

All the risk factors in the adult group were associated with an increased risk of an adverse drug reaction. In the child group, an increase in age was associated with a decreased risk of an adverse drug reaction. In contrast to the adult group, gender was not associated with an increased risk of an adverse drug reaction after controlling for age, number of medications or CDS, and number of pharmacies.

Table 18. Multiple logistic regression models assessing the association of demographic and utilization risk factors on the risk of an ADR: all ages

Full Model[a]	Parameter Estimate	SE	z	p-value	Odds ratio	95% CI lower	95% CI upper
Age	-0.001	0.001	-1.579	0.114	0.999	0.997	1.000
Gender[b]	0.147	0.035	4.212	< 0.001	1.159	1.082	1.241
Medications	0.230	0.006	38.186	< 0.001	1.259	1.244	1.274
Pharmacies	0.332	0.030	11.139	< 0.001	1.393	1.314	1.477
CDS[c]	0.045	0.008	5.935	< 0.001	1.046	1.030	1.061
Constant	-4.622	0.055					

No CDS[a]	Parameter Estimate	SE	z	p-value	Odds ratio	95% CI lower	95% CI upper
Age	-0.0004	0.001	-0.454	0.650	1.000	0.998	1.001
Gender[b]	0.119	0.035	3.448	0.001	1.127	1.053	1.206
Medications	0.253	0.005	54.589	< 0.001	1.288	1.276	1.300
Pharmacies	0.318	0.030	10.711	< 0.001	1.375	1.297	1.457
Constant	-4.624	0.055					

No Meds[a]	Parameter Estimate	SE	z	p-value	Odds ratio	95% CI lower	95% CI upper
Age	0.002	0.001	2.251	0.024	1.002	1.000	1.004
Gender[b]	0.339	0.034	9.998	< 0.001	1.404	1.314	1.500
Pharmacies	0.602	0.029	21.110	< 0.001	1.825	1.726	1.930
CDS[c]	0.218	0.006	39.200	< 0.001	1.244	1.231	1.258
Constant	-4.721	0.055					

[a]The full model included the CDS and the number of medications variables in the same model. Models were repeated using only CDS or only the number of medications variable secondary to correlation between the two variables.

[b] dichotomous coding 0 = male, 1 = female

[c] chronic disease score

Full model: Model Likelihood-Ratio test χ^2 (5) = 3,611.50, $p < 0.001$

No CDS model: Model Likelihood-Ratio test χ^2 (4) = 3,576.87, $p < 0.001$

No Meds model: Model Likelihood Ratio test χ^2 (4) = 2,204.62, $p < 0.001$

Table 19. Multiple logistic regression models assessing the association of demographic and utilization risk factors on the risk of an ADR by child and adult cohorts

<18 years	Parameter Estimate	SE	t	p-value	Odds ratio	95% lower	CI upper
Age	-0.065	0.007	-8.840	<0.001	0.937	0.923	0.950
Gender[a]	-0.007	0.080	-0.083	0.934	0.993	0.850	1.161
Medications	0.361	0.024	15.139	0.000	1.434	1.369	1.503
Pharmacies	0.096	0.087	1.102	0.270	1.101	0.928	1.307
CDS[b]	-0.002	0.025	-0.093	0.926	0.998	0.950	1.047
Constant	-4.065	0.123	-32.963				

≥ 18 years	Parameter Estimate	SE	t	p-value	Odds Ratio	95% lower	CI upper
Age	0.002	0.001	1.376	0.169	1.002	0.999	1.005
Gender[a]	0.208	0.040	5.153	<0.001	1.232	1.138	1.333
Medications	0.222	0.006	35.537	<0.001	1.249	1.233	1.264
Pharmacies	0.350	0.032	10.958	<0.001	1.419	1.333	1.510
CDS[b]	0.045	0.008	5.672	<0.001	1.046	1.030	1.062
Constant	-4.812	0.086	-56.049				

[a] dichotomous coding 0 = male, 1 = female

[b] chronic disease score

Child model N = 27,452, Model Likelihood-Ratio test χ^2 (5) = 407.40, $p < 0.001$

Adult model N = 92,576, Model Likelihood-Ratio test χ^2 (5) = 3,204.75, $p < 0.001$

Table 20. Multiple logistic regression models assessing the association of demographic and utilization risk factors on the risk of an ADR by child and adult cohorts including age, gender, and number of medications interaction terms

<18 years	Parameter estimate	SE	t	p-value	Odds ratio	95% lower	CI upper
Age	-0.091	0.012	-7.491	<0.001	0.913	0.892	0.935
Gender[a]	-0.013	0.079	-0.158	0.875	0.988	0.845	1.154
Medications	0.287	0.034	8.542	<0.001	1.333	1.248	1.424
Pharmacies	0.120	0.088	1.355	0.175	1.127	0.948	1.340
Age*meds[b]	0.009	0.003	2.679	0.007	1.009	1.002	1.015
Constant	-3.893	0.138	-28.149				

≥ 18 years	Parameter estimate	SE	t	p-value	Odds Ratio	95% lower	CI upper
Age	0.018	0.002	8.398	<0.001	1.018	1.014	1.022
Gender[a]	0.356	0.065	5.499	<0.001	1.428	1.258	1.621
Medications	0.457	0.023	19.515	<0.001	1.580	1.509	1.654
Pharmacies	0.291	0.320	8.982	<0.001	1.338	1.255	1.425
Age*meds[b]	-0.003	0.000	-8.881	<0.001	0.997	0.996	0.997
Gender*meds[c]	-0.037	0.011	-3.373	0.001	0.964	0.943	0.985
Constant	-5.649	0.126	-44.805				

[a] dichotomous coding 0 = male, 1 = female

[b] interaction term age*number of medications

[c] interaction term gender*number of medications

Child model N = 27,452, Model Likelihood-Ratio test χ^2 (5) = 414.62, $p < 0.001$

Adult model N = 92,576, Model Likelihood-Ratio test χ^2 (6) = 3,260.89, $p < 0.001$

Table 21. Multiple logistic regression models containing chronic disease score with interaction term in child and adult cohorts

<18 years	Parameter estimate	SE	t	p-value	Odds ratio	95% lower	CI upper
Age	-0.078	0.009	-8.726	< 0.001	0.925	0.909	0.941
Gender[a]	0.017	0.079	0.218	0.827	1.017	0.872	1.187
Pharmacies	0.513	0.080	6.414	< 0.001	1.670	1.428	1.954
CDS	0.071	0.034	2.089	0.037	1.074	1.004	1.147
Age*CDS[b]	0.016	0.004	4.350	< 0.001	1.016	1.001	1.023
Constant	-3.383	0.123	-31.076	< 0.001			

≥ 18 years	Parameter estimate	SE	t	p-value	Odds Ratio	95% lower	CI upper
Age	0.012	0.012	6.988	< 0.001	1.012	1.009	1.015
Gender[a]	0.428	0.039	10.881	< 0.001	1.535	1.421	1.658
Pharmacies	0.601	0.031	19.472	< 0.001	1.824	1.717	1.937
CDS	0.417	0.026	15.782	< 0.001	1.518	1.441	1.599
Age*CDS[b]	-0.004	0.000	-7.673	< 0.001	0.996	0.995	0.997
Constant	-5.276	0.099	-53.057	< 0.001			

[a] dichotomous coding 0 = male, 1 = female

[b] interaction term age*CDS

Child model N = 27,452, Model Likelihood-Ratio test χ^2 (5) = 215.43, $p < 0.001$

Adult model N = 92,576, Model Likelihood-Ratio test χ^2 (5) = 2,048.40, $p < 0.001$

Sub-analysis for risk for hospitalization

An additional analysis examined the association between the occurrence of an adverse drug reaction and the risk of hospitalization. There were 1,071 hospitalizations on or after the index date among the 4,287 adverse drug reaction cases. There were 8,177 hospitalizations on or after the index date among the 115,741 controls. This was a significant difference between cases and controls ($p < 0.001$).

After controlling for the risk factors of age, gender, number of pharmacies, and CDS, those with an adverse drug reaction were 3.1 times as likely to be hospitalized as those who did not have an adverse drug reaction (Table 22).

Table 22. Multiple logistic regression models assessing the association of demographic, utilization, and CDS risk factors on the risk of hospitalization

	Parameter estimate	SE	z	p-value	Odds ratio	95% CI lower	CI upper
ADR[a]	1.141	0.039	29.120	<0.001	3.13	2.90	3.38
Age	0.004	0.001	6.498	<0.001	1.004	1.003	1.005
Gender	0.214	0.023	9.168	<0.001	1.238	1.183	1.296
Pharmacies	0.233	0.025	9.440	<0.001	1.262	1.183	1.296
CDS[b]	0.164	0.004	37.469	<0.001	1.178	1.168	1.188
Constant	-3.391	0.040	-84.467	<0.001			

[a] Adverse drug reaction
[b] Chronic disease score

Sub-analysis of drug class versus diagnosis code in method two

Method two targeted specific drug classes and antidotes. The diagnosis codes corresponding to the targeted drug classes are listed in Table 23. For the anti-infective drug class, GI manifestations comprised the majority (82.2%) of the reactions, followed by the code for an unspecified adverse effect of a drug (11.6%), and allergic/dermatologic reactions (6.2%).

GI hemorrhage accounted for 56 percent of the reactions to warfarin. Gastritis and duodenitis accounted for approximately 31 percent of the reactions to NSAIDs and, as expected, allergic urticaria was the most prevalent outcome in those receiving a corticosteroid – antihistamine combination (29 %).

Table 23. Diagnosis codes by targeted drug classes from method two

Diagnosis Code	Targeted drug class
Targeted outcome with anti-infective use	
008.45 *C. difficile*	38
535.0x Acute gastritis	173
535.4x Other gastritis	57
535.5x Unspecified gastritis	309
558.3 Allergic gastroenteritis	2
693.0 Dermatitis medicamentosa	70
695.1 Erythema multiforme	28
708.0 Allergic urticaria	87
787.0x Nausea/vomiting	1477
995.0 Anaphylactic shock	9
995.1 Angioneurotic edema	37
995.2 Unspecified adverse effect of drug	299
Subtotal	2,586
Targeted outcome with warfarin use	
578.xx Gastrointestinal hemorrhage	36
784.7 Epistaxis	16
786.3 Hemoptysis	12
Subtotal	64
Targeted outcome with NSAID use	
531.xx Gastric ulcer	26
532.xx Duodenal ulcer	10
533.xx Peptic ulcer	72
535.xx Gastritis and duodenitis	325
578.xx GI bleed	147
784.0x Epistaxis	55
787.0x Nausea/vomiting	421
Subtotal	1056
Targeted outcome with glucagon and insulin	
250.8 Diabetes with other specified manifestations	9
Targeted outcome with corticosteroid / antihistamine	
693.0 Dermatitis medicamentosa	8
695.1 Erythema multiforme	1
708.0 Allergic urticaria	18
995.0 Anaphylactic shock	6
995.1 Angioneurotic edema	16
995.2 Unspecified adverse effect of drug	13
Subtotal	62
Targeted outcome with sodium polystyrene sulfonate	
276.7 Hyperpotassemia	2
Total	3,779

Goodness-of-Fit

Summary measures for the goodness-of-fit for the logistic models are shown in Table 24. The areas under the curve in the receiver operating characteristic (ROC) were all above the 0.5 mark with the majority above 0.70. The models, however, as shown by the Hosmer-Lemeshow values, failed to fit the data well. The goodness-of-fit test was not rejected at the 0.05 level for the child models with and without interaction terms.

Table 24. Goodness-of-fit and ROC for regression models

	Hosmer-Lemeshow χ^2-value	p-value	ROC[a]
Table 18. Full group (not age stratified)			
Full model	177.34	<0.001	0.747
No CDS	155.55	<0.001	0.744
No meds	96.30	<0.001	0.677
Table 19. Age stratified; no interaction terms			
Child	14.64	< 0.067	0.700
Adult	159.18	< 0.001	0.761
Table 20. Age stratified; with interaction terms			
Child	13.98	0.082	0.700
Adult	106.66	< 0.001	0.757
Table 21. Age stratified; CDS model with interaction terms			
Child	28.54	0.001	0.649
Adult	35.46	< 0.001	0.694

[a] Receiver operating characteristic

Combined methods: Medical and pharmacy expenditures

Hypothesis 7: There is no difference in expenditures between those identified with an adverse drug reaction and those without an adverse drug reaction.

The effect of an adverse drug reaction on total post-index date expenditures is presented in Tables 25 and 26. After controlling for the demographic characteristics of age, gender, number of medications, and number of pharmacies, as well as the pre-index date pharmacy and medical expenditures, the presence of an adverse drug reaction was significantly associated with an increase in expenditures in both the adult and child groups ($p < 0.001$). All variables were statistically significant in the adult model. Age and number of pharmacies were not significant in the child model.

Table 25. Linear regression analysis of the association between ADR presence, age, gender, number of medications, and number of pharmacies on the log of total expenditures after controlling for pre-index expenditures for the child cohort

	Parameter Estimate	SE	t	p-value	95% CI lower	95% CI upper
ADR	0.407	0.052	7.794	< 0.001	0.305	0.509
Age	0.001	0.002	0.311	0.756	-0.002	0.003
Gender	-0.115	0.017	-6.924	< 0.001	-0.148	-0.083
Medications	0.026	0.007	3.724	< 0.001	0.012	0.040
Pharmacies	0.050	0.026	1.940	0.052	-0.001	0.102
Log (pre-index costs)[a]	0.529	0.007	78.034	< 0.001	0.516	0.543
Constant	2.085	0.043	48.966	< 0.001	2.002	2.169

[a] log of total pre-index date expenditures

Model F (6; 27,452) = 1,260.96, $p < 0.001$, Adjusted $R^2 = 0.2159$

Table 26. Linear regression analysis of the association between ADR presence, age, gender, number of medications, and number of pharmacies on the log of total expenditures after controlling for pre-index expenditures for the adult cohort

	Parameter Estimate	SE	t	p-value	95% CI lower	95% CI upper
ADR	0.572	0.024	24.010	< 0.001	0.525	0.618
Age	0.004	0.001	15.577	< 0.001	0.004	0.006
Gender	0.110	0.010	11.527	< 0.001	0.092	0.129
Medications	0.049	0.002	23.352	< 0.001	0.045	0.053
Pharmacies	0.040	0.012	3.235	0.001	0.016	0.064
Log (pre-index costs)[a]	0.475	0.004	132.387	< 0.001	0.468	0.482
Constant	2.308	0.027	84.629	< 0.001	2.254	2.361

[a] log of total pre-index date expenditures

Model F (6; 92,569) = 4,648.19, $p < 0.001$, Adjusted $R^2 = 0.2315$

Regression diagnostics

Because expenditure data are highly skewed, these variables were log transformed prior to inclusion in the regression models. Although this improved the normality and linearity for most of the expenditure variables, especially the dependent variable (Figure 3 and 4), the models still did not meet the assumptions of normality and linearity, nor did they meet the assumption of homoscedasticity. A graph of the residuals from the model was similarly left skewed. Assessments for multicollinearity were within acceptable ranges with a variance inflation factor (VIF) ranging from 1.03 to 1.54 (mean 1.19) for the adult model and 1.01 to 1.42 (mean 1.15) in the child model.

Figure3: Log transformed post-index date expenditures in the adult model

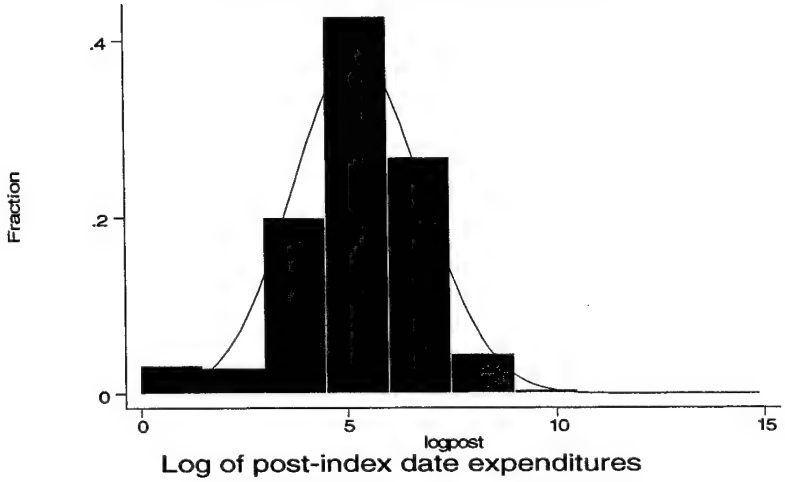
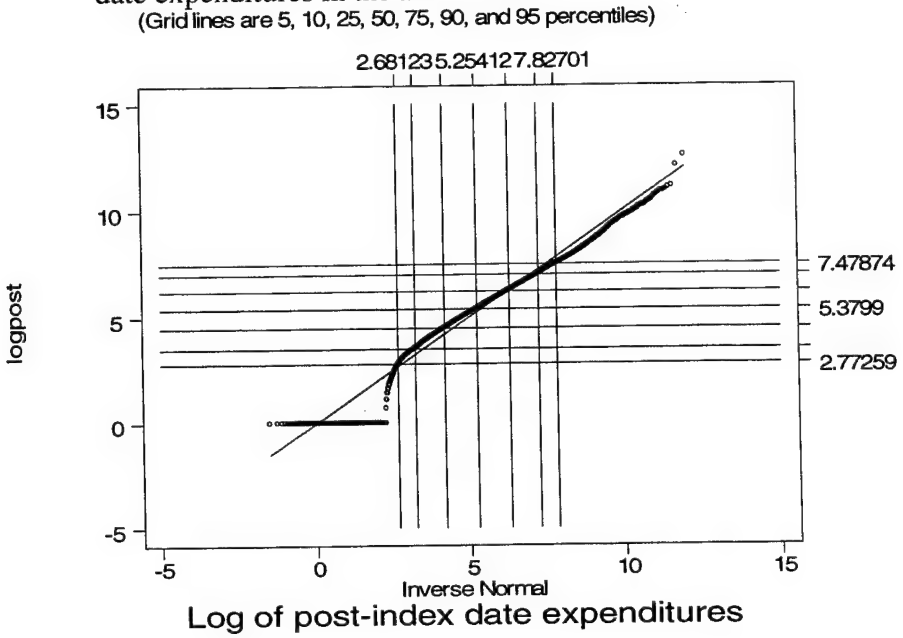


Figure 4: Normal quantile plot: Log-transformed post-index date expenditures in the adult model



CHAPTER 5: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Discussion overview

This section is divided into three major areas: evaluation of the adverse drug reaction detection methods, evaluation of the risk factor analysis, and evaluation of the adverse drug reaction expenditures.

Evaluation of the adverse drug reaction detection methods

Research question one: *Can adverse drug reactions be detected within a claims database using diagnosis codes specific for adverse drug reactions?*

Research question two: *Can adverse drug reactions be detected within a claims database using selected drugs and drug-drug combinations as trigger events?*

The automated screening applied in methods one and two appeared to successfully capture the number of reactions in line with what was anticipated. Targeting ICD-9-CM codes in method one captured 1,649 reactions and targeting specific drugs with method two captured 3,779 reactions. The stringency of the screening criteria resulted in potential reactions being excluded that could have been included had the exposure information been more complete. For example, while by definition the E-coded claims indicated specifically that a medication was responsible for the adverse reaction; the stipulated methods required that a corresponding medication be present in the pharmacy claim file within the previous 30 days. While this screening criterion may appear overly cautious in the circumstance of the E-coded claims, the intent was to reduce the number of false positives produced within the other diagnosis codes. Because

medical records were unavailable to confirm or refute a potential adverse drug reaction, the screening was designed to detect only those events with the strongest level of suspicion given the limits of the data.

Research question three: *Can adverse drug reactions be detected within a claims database using inappropriateness of prescribing criteria as trigger events?*

Although all three methods identified at least some potential adverse drug reactions, method three, targeting inappropriate prescribing, captured the least number with 60 reactions. The low yield of method three could have been caused by several things. First, from a positive perspective, since method three was keyed to identifying reactions that were due to inappropriate prescribing practices, a low yield could be reflective of adherence to prescribing guidelines for these particular diagnosis-drug combinations in this population.

Second, the automated screening mechanism used in this method was particularly stringent. Although confident that the initial diagnosis-drug matching process was comprehensive, the screening criteria applied to the review of the diagnosis codes in the 30-day period after the diagnosis-drug match might have been too narrow to capture the reactions; however, this theory was contradicted when a manual review of all medical claims in this 30-day period produced only a modest change in the screening criteria and a minimal increase in the adverse drug reactions captured.

Third, the timeframe in which the reaction was allowed to become evident was only 30 days. This short time lapse may not have been long enough. For instance the

exacerbation of constipation by a newly prescribed tricyclic antidepressant may not occur until much later, especially if concomitant medications were provided to reduce the risk.

Overall, there is no way to establish what the true sensitivity of these methods is unless a validation using medical record confirmation is conducted. Likewise, the specificity, that is, the number of patients that were allocated to the control group because they tested negative on experiencing an adverse drug reaction, cannot be calculated using only the claims data.

Although much emphasis was placed on reducing the false positives, meaning labeling someone as having an adverse drug reaction when they did not, the lack of complete exposure information was a drawback to both the sensitivity and the specificity of this screening method. Patients were eliminated from the ADR group and the control group because they did not have a drug match within the dedicated 30-day timeframe. This action potentially forced some false negatives into the sample. Also, some potential cases and controls were excluded because they lacked the required 90-days pre and post-index date information upon which the risk factor and expenditure information was drawn.

The number of multiple events (n=1,201) also raised questions about potential false positives in the sample in some cases. While most of the multiple events were due to detection of the same reaction by different methods, there were some instances where the decision rules allowed the same diagnosis code-medication match to be counted more than once in the time period. It was particularly difficult in these circumstances to distinguish between whether the medication contributed to the diagnosis or was being

used as treatment for the diagnosis. By disallowing the same diagnosis code-medication match from being counted more than twice and requiring at least a six month time period between the index dates, this misclassification threat was reduced.

The incidence rate of approximately 2 percent (3.9 percent in adults) over the two years falls within the range of the other retrospective outpatient studies (0.67 to 36 percent) cited in Table 2. Recall that the studies reporting the higher end of the range (35 and 36 percent) included a patient-reported component along with the retrospective pharmacy or medical record review (Hanlon et al., 1997; Meleney & Fraser, 1969). In general, the outpatient studies reporting adverse drug reactions based solely upon patient interview and/or survey responses showed a greater frequency rate than those based solely upon retrospective record reviews (range 4.8 to 41 percent versus 0.67 to 21 percent). Thus, the lower rate in this retrospective review was anticipated, particularly because of the restricted scope. In contrast to some of the other retrospective studies, age groups were not limited nor was a risk status established prior to the study.

The study by Gandhi and colleagues (2000) reporting a 2.8 percent frequency rate was the most comparable to this study in that their study included outpatients between 20 and 75 years of age who had made at least one visit to a primary care physician within the last year and only considered those with reported prescription drug use. Although this study's ages ranged from 0.5 to 97 years, only 4,356 patients (3.7 percent) were 65 years or older. Only 618 patients (0.51 percent) were over age 75, and approximately 23 percent of patients were under age 18.

In summary, all three methods could be used to identify suspected adverse drug reactions. The inability to establish causality and validate the suspicion, however, limits the inferences that can be made from the risk factor analysis.

Evaluation of risk factors

In the combined group, age was not significantly associated with an adverse drug reaction. When age was stratified into the child and adult models it was a significant predictor for an adverse drug reaction. While an increase in age in the child model resulted in the expected decrease in adverse drug reaction risk, the anticipated increase in risk with increasing age in the adult group did not occur ($p = 0.169$) until the regression model was further adjusted for the interaction between age and the number of medications ($p < 0.001$). The evaluation of the adverse drug reactions by age decades showed an increasing frequency with each decade, but the rate declined after age 65. This was most likely due to the lack of TRICARE coverage for those 65 years or older during the timeframe of the study. Under the recent TRICARE-for-Life and Senior Pharmacy plan revisions, this downward trend would seem unlikely to remain if the study were redone using data pulled after the plan revisions were implemented.

Contrary to the Carbonin and colleagues (1991) hospital study, age was significant in the adult model after the interaction term was included. Their study did not include an adjustment factor for the interaction between age and number of medications. They also had a much older group (mean age = 67.1 years) than this study and stratified the number of medications into those taking more than four drugs versus those taking four or less. When the models were repeated categorizing the number of medications as

Carbonin's group, age showed no association ($p = 0.693$) in the adult group. However, when an interaction term between age and number of medications was applied into the model, age was significant ($p < 0.001$).

Although this study would not meet the inclusion criteria for the meta-analysis by Impicciatore and colleagues (2001), the ADR frequency rate in outpatient children does compare to the 1.46 percent incidence rate derived in their study. The decreasing risk with increasing age in the child model concurs with Ajayi's (2000) theory that the very young may be predisposed to adverse drug reactions secondary to their unique pharmacodynamic differences.

The difference in gender diverged between the adult and child models. While unimportant in the child model, adult females consistently experienced a greater risk of an ADR than males did in models with and without interaction terms. Although many of the previous studies did not note a gender effect, those that did, showed a propensity for the females to experience more adverse drug reactions. Thus, this study's results concurred with the previous studies.

An increase in the number of medications had the strongest association with an adverse drug reaction in each model: child or adult, with or without interaction terms.

This study differed from previous studies by its inclusion of the interaction terms to adjust the regression model to account for the interplay between age, gender, co-morbidity, and the number of medications. As previously stated, the number of medications used tends to increase with an increase in age and chronic disease status, as well as, with female gender. Given that the number of medications differed by all three

of these factors in the bivariate analysis in this sample, the addition of an interaction term to the regression model was considered essential to preventing over or under estimation of their association with the adverse drug reaction outcome.

The CDS was the proxy used for co-morbidities. An increase in CDS was assumed to imply an increase in disease severity. The correlation between CDS and the number of medications variable potentially altered the models; therefore, the models were repeated including the CDS variable and its corresponding interaction terms and produced similar results to the alternative models using number of medications (Tables 18, 19, 20, and 21).

Where the model using the CDS variable differed was in the change in the association between the number of pharmacies used and an adverse drug reaction. The CDS variable model showed an increase in the association as compared to the model using the number of medications (OR 1.8 versus OR 1.3 in the adult model; 1.7 versus 1.1 in the child model). Why this change occurred is unclear. Although the mean CDS was greater in those using two or more pharmacies, addition of a CDS*number of pharmacy interaction variable was not significant and resulted in only a small reduction in the pharmacy odds ratio (OR 1.7). A check for multicollinearity was also negative.

By using the parameter coefficient, the change in the odds ratio associated with an incremental change in the number of pharmacies can be calculated. Using the equation $e^{\beta * \text{change in } x}$ and the coefficients for adults in Table 20, an increase in the number of pharmacies to two pharmacies would increase the adverse drug reaction risk 1.79 times ($e^{0.291*2}$). Because the interaction terms were significant between age and number of

medications; gender and number of medications; and CDS and number of medications, the parameter coefficients could not be quantified by this method for the other risk factors.

A sub-analysis assessing the association between having an adverse drug reaction and the risk of hospitalization showed that after controlling for age, gender, number of pharmacies, and CDS, those with an adverse drug reaction had 3.1 times the risk of being hospitalized. Age, gender, number of pharmacies, and CDS were also significantly associated with the risk of hospitalization ($p < 0.001$). This association between CDS and hospitalization risk concurred with the association found by Von Korff and colleagues (Von Korff et al., 1992).

Evaluation of pharmacy and medical expenditures

Interpretation of the expenditure data is particularly difficult because the log transformation required to effect some normality on the dependent variable precludes quantifying the expenditure changes.

A Windsorizing technique that modifies any outliers back to a preset percentile value was an alternative to log-transformation that was attempted, but as this did not help the model meet the assumptions, it was dropped from further analysis.

Conclusions

All three adverse drug reaction identification methods did detect potential adverse drug reactions to varying degrees; therefore, the three research questions as to whether any of these methods could detect adverse drug reactions were affirmed. Caution must

be used, however, since none of the reactions labeled as an adverse drug reaction were actually confirmed through other validated collection methods.

While method three's inappropriate prescribing criterion could have usefulness as a quality assurance tool, it contributed little to this research in attempting to validate ADR risk factors. Methods one and two provided more information but since reactions were restricted to specific diagnosis codes and drug classes, caution should be exercised in extrapolating these results too far from the targeted drug classes and diagnoses codes.

The logistic regression analysis of the adverse drug reaction risk factors yielded results consistent with the majority of existing literature. The use of interaction terms to adjust for the relationship between age, gender, number of medications, and CDS was a study strength. Very few previous researchers attempted to do so. Demonstrating that age, gender, number of medications, and number of pharmacies are significant predictors of an adverse drug reaction subsequent to adjusting for interactions engenders more confidence that the association exists.

While the Hosmer-Lemeshow test indicated the model did not fit the data well, almost all of the ROC curves were above 0.70. A value of 0.5 would indicate no predictive ability. A value of 1.0 would indicate perfect predictive ability. Thus, these models do demonstrate some predictive ability.

The multiple linear regression expenditure model must be used with caution since the data do not meet the desired assumptions of homoscedasticity, linearity, and normality for this statistical test. Although the adjusted R-squared suggests that the model explains 22.7 percent (adult group) of the variation in post-index date log-

expenditures, it can merely be stated that an association was found between the risk factors and increased expenditures after controlling for pre-index date expenditures. How much of an increase that occurs cannot be quantified.

Finally, although the database had important limitations in the exposure data that were well known before this project was begun, it was still important to examine whether certain literature-based risk factors were indeed important to this unique population, especially given the disparities among the results in previous studies. Identifying whether the literature-based risk factors were significant to this population was necessary before any future adverse drug reaction prevention programs could begin.

Recommendations

The major drawback to a study in this particular population was the unknown amount of missing information. Cooperation and sharing of healthcare information between the Regional Contractors and the DoD facilities has steadily improved each year. Within the last two years the MTF pharmacies gained the ability to view prescription profile information on individual patients that provides information on the prescriptions the patient received from the NMOP or a network pharmacy. The reverse is not yet true. The regional pharmacy benefit managers are not able to obtain information on medications or medical services received from the MTF on a per patient basis. Since the services being provided are to a closed population set, the cooperative efforts between the points of service should continue to be encouraged. Capturing the pharmacy information from the MTF's, merging them with the regional contractor data, and repeating the analysis would improve the robustness of the model.

Broadening the scope of the search would also improve this study but at the risk of increasing the false positives. The automatic screening mechanisms used would not be feasible in some of the other medication classes due to the limitations of the medical claims coding process. Ways to refine the searches to produce greater confidence in the causality of the medication to the coded diagnosis should continue to be explored. Modification of Naranjo's algorithm to account for information obtainable within claims data could be one option that would help in more objectively gauging the confidence level of the causality assumptions made in this study.

This study was limited to a more global overview of the adverse drug reactions. Subanalyses of specific drug classes comparing those identified with an adverse drug reaction with those exposed to the same drug class who did not have an adverse drug reaction, may produce interesting results that could further identify if particular patients are more at risk for an adverse drug reaction when exposed to a specific drug class.

Future research

The goal of assessing these risk factors is to use the information to preemptively implement countermeasures to prevent adverse drug reactions. Knowing who is at risk for an adverse drug reaction given the specific demographics of a defined population is key to developing prevention tactics. This research provides the foundation for this next step.

APPENDIX A

TRICARE REGION INFORMATION

Table A1. TRICARE Region Military Treatment Facility Information: Continental United States (TRICARE Management Activity, 2002b)

Region 1 (Northeast)	**Number of MTFs**	**Region 5 (Heartland)**	**Number of MTFs**
Connecticut	1	Illinois	2
District of Columbia	3	Indiana	0
Delaware	1	Kentucky	2
Maine	1	Michigan	0
Maryland	6	Ohio	1
Massachusetts	1	Wisconsin	0
New Hampshire	1	West Virginia	0
New Jersey	2	Total MTFs in region	5
New York	2		
Pennsylvania	1	**Region 6 (Southwest)**	
Rhode Island	1	Arkansas	1
Vermont	0	Oklahoma	4
Northern Virginia	1	Texas	13
Total MTFs in region	21	Western Louisiana	2
		Total MTFs in region	20
Region 2 (Mid Atlantic)			
North Carolina	5	**Region 7/8 (Central)**	
Southern Virginia	11	Arizona	3
Total MTFs in region	16	Colorado	4
		Iowa	0
Region 3 (Southeast)		Idaho	1
Northern Florida	5	Kansas	3
Georgia	8	Minnesota	0
South Carolina	6	Missouri	2
Total MTFs in region	19	Montana	1
		North Dakota	2
Region 4 (Gulfsouth)		Nebraska	1
Alabama	4	New Mexico	4
Eastern Louisiana	1	Nevada	2
Mississippi	5	South Dakota	1
Tennessee	0	Utah	1
Gulfsouth Florida	6	Wyoming	1
Total MTFs in region	16	West Texas	1
		Total MTFs in region	27
Region 9 (Southern CA)			
Southern California	13	**Region 11 (Northwest)**	
Total MTFs in region	13	Alaska	4
		Oregon	1
Region 10 (Golden Gate)		Washington	7
Northern California	7	Total MTFs in region	12
Total MTFs in region	7		

APPENDIX B

APPROVAL LETTER FROM THE HUMAN SUBJECTS' COMMITTEE

Human Subjects Protection Program

THE UNIVERSITY OF
ARIZONA.
TUCSON ARIZONA

1350 N. Vine Avenue
P.O. Box 245137
Tucson, AZ 85724-5137
(520) 626-6721

21 December 2001

Jolaine Draugalis, Ph.D.
Pharmacy Practice and Science
Pharmacy, Rm. 334
PO BOX 210207

RE: **BSC B01.59** IDENTIFYING PREDICTORS OF ADVERSE DRUG REACTIONS AND ASSOCIATED COSTS USING A CLAIMS DATABASE

Dear Dr. Draugalis:

We received your research proposal as cited above. The procedures to be followed in this study pose no more than minimal risk to participating subjects. Regulations issued by the U.S. Department of Health and Human Services [45 CFR Part 46.110(b)] authorize approval of this type project through the expedited review procedures, with the condition(s) that subjects' anonymity be maintained. Although full Committee review is not required, a brief summary of the project procedures is submitted to the Committee for their endorsement and/or comment, if any, after administrative approval is granted. This project is approved effective **21 December 2001** for a period of one year.

The Human Subjects Committee (Institutional Review Board) of the University of Arizona has a current assurance of compliance, number M-1233, which is on file with the Department of Health and Human Services and covers this activity.

Approval is granted with the understanding that no further changes or additions will be made either to the procedures followed or to the consent form(s) used (copies of which we have on file) without the knowledge and approval of the Human Subjects Committee and your College or Departmental Review Committee. Any research related physical or psychological harm to any subject must also be reported to each committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Theodore J. Glattke, Ph.D.
Chair
Social and Behavioral Sciences Human Subjects Committee

TJG:tl
cc: Departmental/College Review Committee

APPENDIX C

MEDICATIONS USED TO SCREEN DIAGNOSIS CODES IN METHOD ONE

Table C1. Drugs associated with aplastic anemia (Klinker et al., 2002)

Acetazolamide	Felbamate	Phenothiazines
Captopril	Furosemide	Phenytoin
Carbamazepine	Gold Salts	Propylthiouracil
Chloramphenicol	Indomethacin	Quinacrine
Chloroquin	Interferon-α	Quinidine
Chlorothiazide	Methimazole	Sulfonamides
Chlorpromazine	Penicillamine	Sulfonylureas
Dapsone	Pentoxifylline	Sulindac
Diclofenac	Phenobarbital	Ticlopidine

Table C2. Drugs associated with agranulocytosis (Klinker et al., 2002)

Acetazolamide	Fosphenytoin	Penicillamine
Allopurinol	Furosemide	Pentazocine
Benzodiazepines	Ganciclovir	Phenothiazines
β-lactam antibiotics	Gentamicin	Phenytoin
Captopril	Gold Salts	Primidone
Carbamazepine	Griseofulvin	Procainamide
Chloramphenicol	Hydralazine	Propranolol
Chlorpropamide	Hydroxychloroquine	Propylthiouracil
Cimetidine	Imipramine	Pyrimethamine
Clindamycin	Isoniazid	Quinine
Clomipramine	Levodopa	Rifampin
Clozapine	Meprobamate	Sulfonamides
Colchicine	Methazolamide	Sulfonylureas
Dapsone	Methimazole	Thiazides
Desipramine	Methyldopa	Ticlopidine
Doxycycline	Metronidazole	Tocainide
Ethacrynic acid	Nitrofurantoin	Tolbutamide
Ethosuximide	Nonsteroidal anti-	Vancomycin
Flucytosine	inflammatory drugs	Zidovudine

Table C3. Drugs associated with drug-induced parkinsonism (Nelson et al., 2002)

Antipsychotics (phenothiazines, butyrophenones, risperidone, and others)
Metoclopramide
Prochlorperazine
Reserpine

Table C4. Drugs associated with drug psychoses (Doering, 2002; Moore, 2002a; Moore, 2002b)

Anticholinergics	Benzodiazepines	Non-barbiturate sedative-hypnotics
Antipsychotics	Corticosteroids	Stimulants
Barbiturates		

Table C5. Drugs associated with other specified gastritis (Chisholm & Jackson, 2002; Garnett & Dukes, 1988)

Bisphosphonates	Ethacrynic acid	Pancrease supplementation
Bromocriptine	Gentian violet	Potassium chloride
Chemotherapeutics	Isoproterenol	Reserpine
Corticosteroids	Nonsteroidal anti-inflammatory drugs	Warfarin
Erythromycin		

Table C6. Drugs associated with dermatitis and allergic urticaria (Lamberg, 2002)

Acetylcysteine	Cyanocobalamin	Penicillin
Allopurinol	Cyclophosphamide	Pentazocine
Amoxicillin	Doxycycline	Phenazopyridine
Ampicillin	Erythromycin	Phenylbutazone
Barbiturates	Gentamicin	Quinidine
Bromhexine hydrochloride	Hydralazine	Trimethoprim/sulfamethoxazole
Cephalosporins	Isoniazid	Vincristine
Cimetidine		

APPENDIX D

METHOD ONE:

DEMOGRAPHICS AND MODELS

Table D1. Method 1: Distribution demographic, utilization, and chronic disease score by ADR and non-ADR groups

Demographics	ADR Cases (n = 1,586)	Comparison Group (n = 118,438)	p-value[a]
< 18 years old (percent)	199 (12.5)	27,257 (23.0)	
≥ 18 years old (percent)	1,387 (87.5)	91,181 (77.0)	< 0.001
Males (percent)	500 (31.5)	46,870 (39.6)	
Females (percent)	1,086 (68.5)	71,568 (60.4)	< 0.001
1) Age < 18 years old			
Males (percent)	123 (61.8)	16,351 (60.0)	
Females (percent)	76 (38.2)	10,906 (40.0)	0.601
2) Age ≥ 18 years old			
Males (percent)	377 (27.2)	30,519 (33.5)	
Females (percent)	1,010 (72.8)	60,662 (66.5)	< 0.001
	Mean (standard deviation)		
Age	45.1 (19.0)	37.9 (20.6)	< 0.001
< 18 years old	7.3 (5.4)	8.6 (5.5)	0.001
≥ 18 years old	50.5 (13.1)	46.6 (14.5)	< 0.001
Number of Medications	5.1 (4.0)	2.6 (2.2)	< 0.001
< 18 years old	2.9 (2.7)	1.9 (1.3)	< 0.001
≥ 18 years old	5.4 (4.0)	2.8 (2.4)	< 0.001
Number of pharmacies	1.3 (0.7)	1.1 (0.4)	< 0.001
< 18 years old	1.2 (0.5)	1.1 (0.3)	0.018
≥ 18 years old	1.3 (0.7)	1.1 (0.4)	< 0.001
Chronic disease score	3.3 (3.3)	1.3 (2.1)	< 0.001
< 18 years old	1.8 (2.4)	0.7 (1.4)	< 0.001
≥ 18 years old	3.6 (3.3)	1.5 (2.2)	< 0.001

[a] t-test for continuous variables; chi-square for categorical variables

Table D2. Method 1: Comparison of claims paid 90 days prior to index date

Service Locale	ADR Cases	Cases	Controls	Controls	p-value[a]
< 18 years (%)	199 (12.5)		27,257 (23.0)		
≥ 18 years (%)	1,387 (87.5)		91,181 (77.0)		< 0.001
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$419.16 (721.60)	$204.00	$156.75 (372.44)	$68.00	< 0.001
< 18 years	$177.35 (448.22)	$61.00	$90.75 (444.13)	$40.00	0.006
≥ 18 years	$453.85 (746.44)	$232.00	$176.48 (345.72)	$81.00	< 0.001
Office visits	$700.61 (2306.98)	$110.00	$140.68 (561.06)	$44.00	< 0.001
< 18 years	$386.59 (1636.17)	$83.00	$104.47 (260.02)	$46.00	0.016
≥ 18 years	$745.66 (2384.88)	$115.00	$151.51 (623.03)	$43.00	< 0.001
Emergency	$177.97 (427.45)	$0.00	$69.76 (246.52)	$0.00	< 0.001
< 18 years	$155.12 (546.31)	$0.00	$50.23 (172.91)	$0.00	0.007
≥ 18 years	$181.25 (407.71)	$6.00	$75.60 (264.29)	$0.00	< 0.001
Inpatient	$311.05 (1200.16)	$0.00	$102.94 (642.41)	$0.00	< 0.001
< 18 years	$379.98 (1476.49)	$0.00	$68.17 (700.29)	$0.00	0.002
≥ 18 years	$301.16 (1155.41)	$0.00	$113.34 (623.70)	$0.00	< 0.001
Other medical	$160.80 (1143.21)	$0.00	$36.60 (932.59)	$0.00	< 0.001
< 18 years	$236.15 (1250.06)	$0.00	$47.75 (1808.06)	$0.00	0.036
≥ 18 years	$149.99 (1127.12)	$0.00	$33.27 (390.44)	$0.00	< 0.001
Total claims	$1769.59 (3545.98)	$542.50	$506.75 (1506.77)	$201.00	< 0.001
< 18 years	$1351.19 (3589.10)	$224.00	361.38 (2178.15)	$142.00	< 0.001
≥ 18 years	$1831.91 (3536.68)	$610.00	$550.20 (1233.96)	$225.00	< 0.001

[a] t-test

Table D3. Method 1: Comparison of claims paid 90 days after index date

Service Locale	ADR Cases	Cases	Controls	Controls	p-value[a]
< 18 years (%)	199 (12.5)		27,257 (23.0)		< 0.001
≥ 18 years (%)	1,387 (87.5)		91,181 (77.0)		
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$523.29 (1058.10)	$207.00	$153.30 (334.89)	$52.00	< 0.001
< 18 years	$186.65 (534.82)	$46.00	$76.86 (215.02)	$15.00	0.004
≥ 18 years	$571.59 (1104.93)	$243.00	$176.14 (359.98)	$66.00	< 0.001
Office visits	$1,000.44 (3201.06)	$140.00	$155.79 (561.40)	$60.00	< 0.001
< 18 years	$549.79 (2742.10)	$83.00	$114.74 (214.90)	$58.00	0.026
≥ 18 years	$1,065.10 (3257.37)	$153.00	$168.06 (628.43)	$61.00	< 0.001
Emergency	$172.57 (413.89)	$21.00	$75.47 (244.79)	$0.00	< 0.001
< 18 years	$149.87 (510.43)	$0.00	$51.24 (169.10)	$0.00	0.007
≥ 18 years	$175.83 (398.24)	$22.00	$82.72 (262.80)	$0.00	< 0.001
Inpatient	$274.23 (1071.91)	$0.00	$68.73 (451.54)	$0.00	< 0.001
< 18 years	$370.66 (1734.08)	$0.00	$22.53 (274.86)	$0.00	0.005
≥ 18 years	$260.39 (939.61)	$0.00	$82.55 (491.34)	$0.00	< 0.001
Other medical	$214.30 (1772.62)	$0.00	$30.28 (1034.18)	$0.00	< 0.001
< 18 years	$332.27 (1583.73)	$0.00	$46.05 (2071.58)	$0.00	0.012
≥ 18 years	$197.37 (1797.99)	$0.00	$25.57 (326.06)	$0.00	< 0.001
Total claims	$2184.83 (4640.75)	$671.50	$483.53 (1416.40)	$214.00	< 0.001
< 18 years	$1589.25 (5163.41)	$226.00	$311.40 (2163.52)	$137.00	< 0.001
≥ 18 years	$2270.28 (4556.52)	$766.00	$534.99 (1093.25)	$246.00	< 0.001

[a] t-test

Table D4. Method 1: Multiple logistic regression models for child and adult groups without interaction terms

Variable	Parameter Estimate	SE	t	P-value	Odds Ratio	95% CI Lower	CI Upper
Combined group							
Age	-0.001	0.001	-1.579	0.114	0.999	0.997	1.000
Gender	0.147	0.035	4.212	<0.001	1.159	1.081	1.241
Medications	0.230	0.006	38.186	<0.001	1.259	1.244	1.274
Pharmacies	0.332	0.030	11.139	<0.001	1.393	1.314	1.477
CDS	0.445	0.008	5.935	<0.001	1.046	1.030	1.061
Constant	-4.1622	0.055	-84.211				
< 18 years old							
Age	-0.043	0.013	-3.217	0.001	0.957	0.933	0.983
Gender	-0.033	0.148	-0.221	0.825	0.967	0.725	1.293
Medications	0.218	0.040	5.442	<0.001	1.244	1.150	1.346
Pharmacies	0.026	0.166	0.157	0.875	1.026	0.741	1.421
CDS	0.169	0.040	4.223	<0.001	1.184	1.095	1.280
Constant	-5.281	0.231	-22.848				
≥ 18 years old							
Age	0.005	0.002	2.307	0.021	1.005	1.001	1.009
Gender	0.267	0.063	4.247	<0.001	1.306	1.154	1.476
Medications	0.123	0.009	13.296	<0.001	1.130	1.110	1.151
Pharmacies	0.386	0.043	8.887	<0.001	1.471	1.351	1.601
CDS	0.141	0.012	12.175	<0.001	1.151	1.125	1.178
Constant	-5.866	0.134	-43.701				

Group model N = 120,024, Model Likelihood-Ratio test χ^2 (5) = 3,611.50, $p < 0.001$
Child model N = 27,456, Model Likelihood-Ratio test χ^2 (5) = 106.15, $p < 0.001$
Adult model N = 92,568, Model Likelihood-Ratio test χ^2 (5) = 1,154.79, $p < 0.001$

Table D5. Method 1: Correlation matrix between the independent variables; adults

(n=92,834)	Age	Gender	Meds	Pharmacies	CDS[a]
Age	1.00				
Gender	-0.12	1.00			
Medications	0.20	0.07	1.00		
Pharmacies	-0.03	0.03	0.23	1.00	
CDS[a]	0.30	-0.07	0.59	0.08	1.00

[a] Chronic disease score

Table D6. Method 1: Correlation matrix between the independent variables; child

(n=27,456)	Age	Gender	Meds	Pharmacies	CDS[a]
Age	1.00				
Gender	0.02	1.00			
Medications	0.03	-0.02	1.00		
Pharmacies	-0.06	-0.01	0.31	1.00	
CDS[a]	-0.01	-0.05	0.44	0.12	1.00

[a] Chronic disease score

Table D7. Method 1: Multiple logistic regression models for child and adult groups with interaction terms

	Parameter Estimate	SE	t	p-value	Odds Ratio	95% CI lower	CI upper
<18 years							
Age	-0.08	0.02	-3.925	<0.001	0.921	0.884	0.959
Gender[a]	-0.09	0.15	-0.576	0.565	0.919	0.687	1.227
Medications	0.20	0.07	2.981	0.003	1.216	1.069	1.383
Pharmacies	0.06	0.17	0.374	0.708	1.066	0.763	1.489
Age*meds[b]	0.01	0.01	2.172	0.030	1.012	1.001	1.024
Constant	-4.99	0.26	-19.144				

	Parameter Estimate	SE	t	p-value	Odds ratio	95% CI lower	CI upper
≥ 18 years							
Age	0.024	0.003	7.484	<0.001	1.024	1.018	1.031
Gender[a]	0.426	0.096	4.427	<0.001	1.531	1.268	1.848
Medications	0.407	0.034	12.116	<0.001	1.503	1.407	1.605
Pharmacies	0.289	0.044	6.527	<0.001	1.336	1.224	1.457
Age*meds[b]	-0.003	0.001	-5.706	<0.001	0.997	0.996	0.998
Gender*meds[c]	-0.051	0.015	-3.330	0.001	0.950	0.922	0.979
Constant	-6.791	0.191	-35.530				

[a] dichotomous coding 0 = male, 1 = female
[b] interaction term age*number of medications
[c] interaction term gender*number of medications

APPENDIX E

METHOD TWO:

DEMOGRAPHICS AND MODELS

Table E1. Method 2: Distribution demographic, utilization, and chronic disease score by ADR and non-ADR groups

Demographics	ADR Cases n = 3,361	Comparison Group n = 116,667	p-value[a]
< 18 years old (percent)	637 (19.0)	26,815 (23.0)	
≥ 18 years old (percent)	2,724 (81.0)	89,852 (77.0)	< 0.001
Sex (percent)			
Males	1,075 (32.0)	46,298 (39.7)	
Females	2,286 (68.0)	70,369 (60.3)	< 0.001
1) Age < 18 years old			
Males (percent)	383 (60.1)	16,087 (60.0)	
Females (percent)	254 (39.9)	10,728 (40.0)	0.946
2) Age ≥ 18 years old			
Males (percent)	692 (25.4)	3,0211 (33.6)	
Females (percent)	2,032 (74.6)	59,641 (66.4)	< 0.001
	Mean (standard deviation)		
Age	40.95 (21.12)	37.88 (20.59)	< 0.001
< 18 years old	6.5 (5.5)	8.6 (5.4)	0.001
≥ 18 years old	49.0 (14.2)	46.6 (14.5)	< 0.001
Number of Medications	5.4 (4.1)	2.5 (2.2)	< 0.001
< 18 years old	3.0 (2.5)	1.9 (1.2)	< 0.001
≥ 18 years old	6.0 (4.2)	2.7 (2.3)	< 0.001
Number of Pharmacies	1.3 (0.7)	1.1 (0.4)	< 0.001
< 18 years old	1.2 (0.5)	1.1 (0.3)	< 0.001
≥ 18 years old	1.3 (0.7)	1.1 (0.4)	< 0.001
Chronic Disease Score	2.7 (3.1)	1.3 (2.0)	< 0.001
< 18 years old	1.2 (2.0)	0.7 (1.4)	< 0.001
≥ 18 years old	3.0 (3.2)	1.5 (2.2)	< 0.001

[a] t-test for continuous variables; chi-square for categorical variables

Table E2. Method 2: Comparison of claims paid 90 days before index date

Service Locale	ADR Cases	Cases	Controls	Controls	p-value[a]
< 18 years (%)	637 (19.0)		26,815 (23.0)		
≥ 18 years (%)	2,724 (81.0)		89,852 (77.0)		< 0.001
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$371.77 (677.50)	$167.00	$154.78 (368.66)	$67.00	< 0.001
< 18 years	$137.15 (575.20)	$44.00	$90.84 (448.00)	$40.00	0.044
≥ 18 years	$426.63 (687.91)	$223.50	$173.86 (339.10)	$80.00	< 0.001
Office visits	$420.87 (1834.99)	$93.00	$139.60 (536.82)	$44.00	< 0.001
< 18 years	$169.51 (421.82)	$82.00	$104.00 (253.78)	$46.00	< 0.001
≥ 18 years	$479.64 (2023.64)	$96.00	$150.22 (595.37)	$43.00	< 0.001
Emergency	$137.28 (353.80)	$0.00	$68.92 (245.35)	$0.00	< 0.001
< 18 years	$91.42 (325.24)	$0.00	$49.63 (171.12)	$0.00	0.001
≥ 18 years	$148.01 (359.37)	$10.00	$74.68 (263.21)	$0.00	< 0.001
Inpatient	$230.10 (1064.98)	$0.00	$101.95 (640.35)	$0.00	< 0.001
< 18 years	$108.07 (640.25)	$0.00	$69.16 (710.52)	$0.00	0.131
≥ 18 years	$258.63 (1139.94)	$0.00	$111.74 (617.55)	$0.00	< 0.001
Other medical	$89.12 (626.99)	$0.00	$36.15 (938.71)	$0.00	< 0.001
< 18 years	$95.63 (828.76)	$0.00	$47.62 (1823.39)	$0.00	0.167
≥ 18 years	$87.60 (569.78)	$0.00	$32.73 (389.74)	$0.00	< 0.001
Total claims	$1249.13 (2736.56)	$450.00	$501.40 (1503.62)	$199.00	< 0.001
< 18 years	$601.77 (1737.19)	$201.00	$361.24 (2204.16)	$141.00	< 0.001
≥ 18 years	$1400.51 (557.50)	$557.50	$543.23 (1215.79)	$222.00	< 0.001

[a] t-test

Table E3. Method 2: Comparison of claims paid 90 days after index date

Service Locale	ADR Cases	Cases	Controls	Controls	p-value[a]
< 18 years (%)	637 (19.0)		26,815 (23.0)		
≥ 18 years (%)	2,724 (81.0)		89,852 (77.0)		
					< 0.001
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$406.93 (792.94)	$176.00	$151.01 (331.07)	$51.00	< 0.001
< 18 years	$116.37 (312.63)	$28.00	$76.66 (215.68)	$15.00	0.002
≥ 18 years	$474.87 (853.60)	$238.50	$173.20 (355.38)	$65.00	< 0.001
Office visits	$557.70 (2216.36)	$116.00	$156.00 (566.27)	$60.00	< 0.001
< 18 years	$207.04 (951.32)	$97.00	$115.24 (245.84)	$58.00	0.015
≥ 18 years	$639.70 (2411.33)	$123.00	$168.16 (630.62)	$60.00	< 0.001
Emergency	$180.60 (342.52)	$54.00	$74.33 (244.06)	$0.00	< 0.001
< 18 years	$111.54 (244.47)	$30.00	$50.36 (168.72)	$0.00	< 0.001
≥ 18 years	$196.75 (359.76)	$61.00	$81.49 (261.95)	$0.00	< 0.001
Inpatient	$253.78 (995.66)	$0.00	$67.27 (444.78)	$0.00	< 0.001
< 18 years	$162.41 (1360.76)	$0.00	$22.50 (277.06)	$0.00	0.010
≥ 18 years	$275.15 (887.89)	$0.00	$80.63 (482.90)	$0.00	< 0.001
Other medical	$129.67 (853.51)	$0.00	$29.91 (1042.74)	$0.00	< 0.001
< 18 years	$147.18 (1452.43)	$0.00	$45.91 (2087.08)	$0.00	0.086
≥ 18 years	$125.58 (637.25)	$0.00	$25.13 (334.35)	$0.00	< 0.001
Total claims	$1582.60 (3087.69)	$612.00	$478.47 (1424.07)	$212.00	< 0.001
< 18 years	$744.49 (2540.81)	$248.00	$310.64 (2184.94)	$136.00	< 0.001
≥ 18 years	$1711.96 (3174.72)	$741.00	$528.56 (1094.35)	$243.00	< 0.001

[a] t-test

Table E4. Method 2: Multivariate logistic regression models for child and adult groups

	Parameter Estimate	SE	t	p-value	Odds ratio	95% CI lower	95% CI upper
<18 years							
Age	-0.076	0.008	-9.722	<0.001	0.927	0.913	0.941
Gender[a]	0.010	0.083	0.124	0.901	1.010	0.858	1.190
Medications	0.378	0.025	15.257	<0.001	1.460	1.390	1.532
Pharmacies	0.069	0.092	0.746	0.456	1.071	0.894	1.283
CDS[b]	-0.039	0.027	-1.450	0.147	0.962	0.913	1.014
Constant	-4.075	0.129	-31.649				

	Parameter Estimate	SE	t	p-value	Odds ratio	95% CI lower	95% CI upper
≥ 18 years							
Age	-0.001	0.002	-0.861	0.389	0.999	0.996	1.002
Gender[a]	0.204	0.047	4.370	<0.001	1.226	1.119	1.343
Medications	0.257	0.007	37.433	<0.001	1.293	1.276	1.311
Pharmacies	0.264	0.035	7.583	<0.001	1.302	1.216	1.394
CDS[b]	-0.006	0.009	-0.614	0.539	0.994	0.977	1.012
Constant	-4.890	0.096	-51.062				

[a] dichotomous coding 0 = male, 1 = female

[b] chronic disease score

Table E5. Method 2: Correlation matrix; children

	Age	Gender	Medications	Pharmacies	CDS[a]
Age	1.00				
Gender	0.02	1.00			
Medications	0.03	-0.01	1.00		
Pharmacies	-0.05	-0.01	0.31	1.00	
CDS[a]	-0.01	-0.05	0.44	0.13	1.00

[a] Chronic disease score

Table E6. Method 2: Correlation matrix ; adults

	Age	Gender	Medications	Pharmacies	CDS[a]
Age	1.00				
Gender	-0.12	1.00			
Medications	0.20	0.07	1.00		
Pharmacies	-0.02	0.03	0.24	1.00	
CDS[a]	0.30	-0.07	0.59	0.08	1.00

[a] Chronic disease score

Table E7. Method 2: Multiple logistic regression models for child and adult groups with interaction terms

	Parameter Estimate	SE	t	p-value	Odds ratio	95% CI lower	CI upper
<18 years							
Age	-0.101	0.013	-7.968	<0.001	0.904	0.881	0.926
Gender	0.012	0.083	0.147	0.884	1.012	0.860	1.192
Medications	0.287	0.034	8.343	<0.001	1.332	1.246	1.425
Pharmacies	0.093	0.093	0.992	0.321	1.097	0.914	1.317
Age*meds[b]	0.009	0.003	2.590	0.010	1.009	1.002	1.016
Constant	-3.902	0.144	-27.127				

	Parameter Estimate	SE	t	p-value	Odds ratio	95% CI lower	CI upper
≥ 18 years							
Age	0.013	0.002	5.379	<0.001	1.013	1.008	1.018
Gender	0.350	0.074	4.725	<0.001	1.420	1.228	1.642
Medications	0.455	0.025	18.054	<0.001	1.576	1.500	1.656
Pharmacies	0.220	0.036	6.188	<0.001	1.246	1.162	1.335
Age*meds[b]	-0.003	0.000	-8.026	<0.001	0.997	0.996	0.997
Gender*meds[c]	-0.029	0.012	-2.416	0.016	0.971	0.949	0.995
Constant	-5.659	0.140	-40.354				

[a] dichotomous coding 0 = male, 1 = female
[b] interaction term age*number of medications
[c] interaction term gender*number of medications

APPENDIX F

METHOD THREE:

DEMOGRAPHICS

Table F1. Method 3: Distribution demographic, utilization, and chronic disease score

Demographics	ADR Cases (n = 60)
< 18 years old (%)	3 (5)
≥ 18 years old (%)	57 (95)
Males (%)	17 (28.3)
Females (%)	43 (71.7)
1) Age < 18 years old	
Males (%)	1 (33.3)
Females (%)	2 (66.7)
2) Age ≥ 18 years old	
Males (%)	16 (28.1)
Females (%)	41 (71.9)
Mean (standard deviation)	
Age	53.9 (14.9)
< 18 years old	13.3 (2.1)
≥ 18 years old	56.0 (11.6)
Number of medications	8.5 (4.7)
< 18 years old	7.3 (5.9)
≥ 18 years old	8.5 (4.7)
Number of pharmacies	1.2 (0.5)
< 18 years old	1.0 (0.0)
≥ 18 years old	1.2 (0.5)
Chronic disease score	5.3 (4.0)
< 18 years old	2.7 (3.1)
≥ 18 years old	5.4 (4.0)

Table F2. Method 3: Claims paid for cases 90 days before and after index date

Service Locale	Before index date		After index date expenditures		p-value[a]
	Mean (SD)	Median	Mean (SD)	Median	
Pharmacy	$639.12 (1102.78)	$382.50	$583.53 (557.41)	$414.00	0.664
< 18 years	$382.33 (176.32)	$402.00	$370.00 (472.66)	$196.00	0.953
≥ 18 years	$652.63 (1129.80)	$379.00	$594.77 (562.85)	$423.00	0.667
Office visits	$426.85 (876.87)	$180.50	$327.93 (649.90)	$145.50	0.281
< 18 years	$499.33 (590.30)	$289.00	$154.33 (168.97)	$78.00	0.293
≥ 18 years	$423.04 (892.95)	$163.00	$337.07 (665.04)	$146.00	0.370
Emergency	$124.65 (209.01)	$28.00	$178.18 (284.08)	$79.50	0.241
< 18 years	$75.00 (129.90)	$0.00	$90.67 (126.36)	$37.00	0.910
≥ 18 years	$127.26 (212.81)	$31.00	$182.79 (289.87)	$80.00	0.245
Inpatient	$531.02 (222.50)	$0.00	$411.23 (1020.51)	$0.00	0.653
< 18 years	$0.00 (0.00)	$0.00	$0.00 (0.00)	$0.00	0.00
≥ 18 years	$558.96 (2277.77)	$0.00	$432.88 (1042.93)	$0.00	0.653
Other medical	$71.07 (217.49)	$0.00	$75.02 (188.54)	$0.00	0.893
< 18 years	$1.67 (2.89)	$0.00	$113.67 (168.29)	$0.00	0.371
≥ 18 years	$74.72 (222.63)	$0.00	$72.98 (190.68)	$0.00	0.955
Total claims	$1792.70 (3503.23)	$979.20	$1575.83 (1509.80)	$1278.50	0.583
< 18 years	$958.33 (672.05)	$711.00	$728.67 (582.88)	$775.00	0.503
≥ 18 years	$1836.61 (3588.13)	$992.00	$1620.42 (1532.64)	$1339.00	0.603

[a] paired t-test

APPENDIX G

MEDICAL CLAIMS BY PLACE OF SERVICE

Table G1. Medical and pharmacy claims included in raw dataset by place of service

Place of Service	Number of claims
Pharmacy	3,968,579
Physician's office	6,122,795
Outpatient hospital (emergency)	1,858,164
Inpatient hospital	1,003,635
Other medical	
Independent lab	678,048
Ambulance	142,573
Patient's home	132,911
Skilled nursing facility	7,067
Ambulatory surgical center	3,848
Nursing home	2,934
Other locations	208
Day care facility	98
Specialized treatment	16

REFERENCES

Abt, K., Cockburn, I.T.R., Guelich, A., & Krupp, P. (1989). Evaluation of adverse drug reactions by means of the life table method. *Drug Information Journal, 23,* 143-149.

Ajayi, F.O., Sun, H., & Perry, J. (2000). Adverse drug reactions: a review of relevant factors. *Journal of Clinical Pharmacology, 40,* 1093-1101.

American Society of Health-System Pharmacists (1998). Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions. *American Journal of Health-System Pharmacy, 55,* 165-166.

Anderson, G.M., Beers, M.H., & Kerluke, K. (1997). Auditing prescription practice using explicit criteria and computerized drug benefit claims data. *Journal of Evaluation in Clinical Practice, 3,* 283-294.

Armstrong, E.P. & Manuchehri, F. (1997). Ambulatory care databases for managed care organizations. *American Journal of Health-System Pharmacy, 54,* 1973-1983.

Atkin, P.A. & Shenfield, G.M. (1995). Medication-related adverse reactions and the elderly: a literature review. *Adverse Drug Reactions & Toxicologic Reviews, 14,* 175-191.

Atkinson AJ (2002). Introduction to principles of clinical pharmacology. Accessed on 4-11-2002, http:www.cc.nih.gov/ccc/principles/pdf/00-01/AAtkinson-010906.pdf.

Auriche, M. & Loupi, E. (1993). Does proof of causality ever exist in pharmacovigilance? *Drug Safety, 9,* 230-235.

Azaz-Livshits, T., Levy, M., Sadan, B., Shalit, M., Geisslinger, G., & Brune, K. (1998). Computerized surveillance of adverse drug reactions in hospital: pilot study. *British Journal of Clinical Pharmacology, 45,* 309-314.

Bates, D.W. (1998). Drugs and adverse drug reactions. How worried should we be? *Journal of the American Medical Association, 279,* 1216-1217.

Bates, D.W., Boyle, D.L., Vander Vleit, M.B., Schneider, J., & Leape, L.L. (1995). Relationship between medication errors and adverse drug events. *Journal of General Internal Medicine, 10,* 199-205.

Bates, D.W., Leape, L.L., & Petrycki, S. (1993). Incidence and preventability of adverse drug events in hospitalized adults. *Journal of General Internal Medicine, 8,* 289-294.

Bates, D.W., Miller, E.B., Cullen, D.J., Burdick, E., Williams, L., Laird, N. et al. (1999). Patient risk factors for adverse drug events in hospitalized patients. *Archives of Internal Medicine, 159,* 2553-2560.

Bates, D.W., O'Neil, A.C., Boyle, D., Teich, J.M., Chertow, G.M., Komaroff, A.L. et al. (1994). Potential identifiability and preventability of adverse events using information systems. *Journal of the American Medical Informatics Association, 1,* 404-411.

Bates, D.W., Spell, N., Cullen, D.J., Burdick, E., Laird, N., Petersen, L.A. et al. (1997). The costs of adverse drug events in hospitalized patients. *Journal of the American Medical Association, 277,* 307-311.

Beard, K. (1992). Adverse reactions as a cause of hospital admission in the aged. *Drugs & Aging, 2,* 356-367.

Beers, M.H. (1997). Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. *Archives of Internal Medicine, 157,* 1531-1536.

Begaud, B., Moride, Y., Tubert-Bitter, P., Chaslerie, A., & Haramburu, F. (1994). False-positives in spontaneous reporting: should we worry about them? *British Journal of Clinical Pharmacology, 38,* 401-404.

Bennett, B.S. & Lipman, A.G. (1977). Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse drug reactions. *American Journal of Hospital Pharmacy, 34,* 931-936.

Bergman, U. & Wiholm, B.E. (1981). Drug-related problems causing admission to a medical clinic. *European Journal of Clinical Pharmacology, 20,* 193-200.

Berry, L.L., Segal, R., Sherrin, T.P., & Fudge, K.A. (1988). Sensitivity and specificity of three methods of detecting adverse drug reactions. *American Journal of Hospital Pharmacy, 45,* 1534-1539.

Bootman, J.L., Harrison, D.L., & Cox, E. (1997). The health care cost of drug-related morbidity and mortality in nursing facilities. *Archives of Internal Medicine, 157,* 2089-2096.

Bordet, R., Gautier, S., LeLouet, H., DuPuis, B., & Caron, J. (2001). Analysis of the direct cost of adverse drug reactions in hospitalized patients. *European Journal of Clinical Pharmacology, 56,* 935-941.

Brennan, T.A., Leape, L.L., Laird, N., Hebert, L., Localio, A.R., Lawthers, A.G. et al. (1991). Incidence of adverse events and negligence in hospitalized patients: Results of the Harvard Medical Practice Study I. *New England Journal of Medicine, 324,* 370-376.

Brown, S.D. & Landry, F.J. (2001). Recognizing, reporting, and reducing adverse drug reactions. *Southern Medical Journal, 94,* 370-373.

Cadieux, R.J. (1989). Drug interactions in the elderly. How multiple drug use increases risk exponentially. *Postgraduate Medicine, 86,* 179-186.

Caranasos, G.J., Stewart, R.B., & Cluff, L.E. (1974). Drug-induced illness leading to hospitalization. *Journal of the American Medical Association, 228,* 713-717.

Carbonin, P., Pahor, M., Bernabei, R., & Sgadari, A. (1991). Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? *Journal of the American Geriatric Society, 39,* 1093-1099.

Carson, J.L., Strom, B.L., Duff, A., Gupta, A., Shaw, M., & Das, K. (1992). The feasibility of studying drug-induced acute hepatitis with use of medicaid data. *Clinical Pharmacology & Therapeutics, 52,* 214-219.

Carson, J.L., Strom, B.L., Soper, K.A., West, J.L., & Morse, M.L. (1987). The association of nonsteroidal antiinflammatory drugs with upper gastrointestinal tract bleeding. *Archives of Internal Medicine, 147,* 85-88.

Case, R.L. & Guzzetti, P.J. (1986). A survey of adverse drug reaction reporting programs in select hospitals. *Hospital Pharmacy, 21,* 423-434.

Castleden, C.M. & Pickles, H. (1988). Suspected adverse drug reactions in elderly patients reported to the committee on safety of medicines. *British Journal of Clinical Pharmacology, 26,* 347-353.

Centers for Disease Control and Prevention (1994). Update: external cause-of-injury coding in hospital discharge data—United States, 1994. *MMWR, 43,* 465-467.

Centers for Disease Control and Prevention (1997). Recommended framework for presenting injury mortality data. *MMWR, 46,* 1-39.

Chisholm, M. & Jackson, M. (2002). Evaluation of the gastrointestinal tract. In J.DiPiro, R. Talbert, G. Yee, G. Matzke, B. Wells, & L. Posey (Eds.), *Pharmacotherapy: A Pathophysiologic Approach* (5th ed., pp. 575-584). New York: McGraw-Hill.

Chrischilles, E.A., Segar, E.T., & Wallace, R.B. (1992). Self-reported adverse drug reactions and related resource use. *Annals of Internal Medicine, 117,* 634-640.

Chyka, P.A. (2000). How many deaths occur annually from adverse drug reactions in the United States? *American Journal of Medicine, 109,* 122-130.

Classen, D.C., Pestotnik, S.L., Evans, R.S., & Burke, J.P. (1991). Computerized surveillance of adverse drug events in hospital patients. *Journal of the American Medical Association, 266,* 2847-2851.

Classen, D.C., Pestotnik, S.L., Evans, R.S., Lloyd, J.F., & Burke, J.P. (1997). Adverse drug events in hospitalized patients, excess length of stay, extra costs, and attributable mortality. *Journal of the American Medical Association, 277,* 301-306.

Col, N., Fanale, J.E., & Kronholm, P. (1990). The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Archives of Internal Medicine, 150,* 841-845.

Collet, J.P., Schaubel, D., Hanley, J., Sharpe, C., & Boivin, J.F. (1998). Controlling confounding when studying large pharmacoepidemiologic databases: a case study of the two-stage sampling design. *Epidemiology, 9,* 309-315.

Colley, C.A. & Lucas, L.M. (1993). Polypharmacy: the cure becomes the disease. *Journal of General Internal Medicine, 8,* 278-283.

Colt, H.G. & Shapiro, A.P. (1989). Drug-induced illness as a cause for admission to a community hospital. *Journal of the American Geriatric Society, 37,* 323-326.

Cooper, J.W. (1999). Adverse drug reaction-related hospitalizations of nursing facility patients: a 4-year study. *Southern Medical Journal, 92,* 485-490.

Corr, K. & Stoller, R. (1996). Adverse drug event reporting at Veterans Affairs facilities. *American Journal of Health-System Pharmacy, 53,* 314-315.

Cullen, D.J., Sweitzer, B.J., Bates, D.W., Burdick, E., Edmondson, A.C., & Leape, L.L. (1997). Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Critical Care Medicine, 25,* 1289-1297.

Dartnell, J.G.A., Anderson, R.P., Chohan, V., Galbraith, K.J., Lyon, M.E.H., Nestor, P.J. et al. (1996). Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. *Medical Journal of Australia, 164,* 659-662.

Dennehy, C.E., Kishi, D.T., & Louie, C. (1996). Drug-related illness in emergency department patients. *American Journal of Health-System Pharmacy, 53,* 1422-1426.

Doering, P. (2002). Substance-related disorders: overview and depressants, stimulants, and hallucinogens. In J.DiPiro, R. Talbert, G. Yee, G. Matzke, B. Wells, & L. Posey (Eds.), *Pharmacotherapy: A Pathophysiologic Approach* (5th ed., pp. 1183-1202). New York: McGraw-Hill.

Drici, M.D. & Clement, N. (2001). Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Safety, 24,* 575-585.

Easton, K.L., Parsons, B.J., Starr, M., & Brien, J.E. (1998). The incidence of drug-related problems as a cause of hospital admissions in children. *Medical Journal of Australia, 169,* 356-359.

Ebbesen, J., Buajordet, I., Erikssen, J., Brørs, O., Hilberg, T., Svaar, H. et al. (2001). Drug-related deaths in a department of internal medicine. *Archives of Internal Medicine, 161,* 2317-2323.

Edlavitch, S.A. (1988). Postmarketing surveillance methodologies. *Drug Intelligence & Clinical Pharmacy, 22,* 68-78.

Edwards, I.R. & Aronson, J.K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet, 356,* 1255-1259.

Ernst, F.R. & Grizzle, A.J. (2001). Drug-related morbidity and mortality: updating the cost-of-illness model. *Journal of the American Pharmacy Association, 41,* 192-199.

Faich, G.A. & Stadel, B.V. (1989). The future of automated record linkage for postmarketing surveillance: a response to Shapiro. *Clinical Pharmacology & Therapeutics, 46,* 387-389.

Fattinger, K., Roos, M., Vergeres, P., Holenstein, C., Kind, B., Masche, U. et al. (2000). Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *British Journal of Clinical Pharmacology, 49,* 158-167.

Field, T.S., Gurwitz, J.H., Avorn, J., McCormick, D., Jain, S., Eckler, M. et al. (2001). Risk factors for adverse drug events among nursing home residents. *Archives of Internal Medicine, 161,* 1629-1634.

Fincham, J.E. (1991). An overview of adverse drug reactions. *American Pharmacy, NS31,* 47-53.

Finn, B. & Carlstedt, B.C. (1995). Reporting adverse drug reactions in an ambulatory care setting. *American Journal of Health-System Pharmacy, 52,* 2704-2706.

First Databank (Medispan) (1999). Generic product identifier [Computer software]. Indianapolis, IN: First Databank (Medispan).

Fletcher, A.P. (1991). Spontaneous adverse drug reaction reporting vs event monitoring: a comparison. *Journal of the Royal Society of Medicine, 84,* 341-344.

Food and Drug Administration (2001). The clinical impact of adverse event reporting: postmarketing reporting of adverse events. http://www.fda.gov/medwatch/articles/medcont/postrep.htm.

French, D.G. (1996). Avoiding adverse drug reactions in the elderly patient: issues and strategies. *Nurse Practitioner, 21,* 90-105.

Friedman, G.D., Collen, M.F., Harris, L.E., Van Brunt, E.E., & deBoer, A. (1971). Experience in monitoring drug reactions in outpatients. The Kaiser-Permanente drug monitoring systems. *Journal of the American Medical Association, 217,* 567-572.

Gabrieli, E.R., Gabrieli, J.D.E., & Rosen, T.J. (1985). Automated monitoring of adverse drug reactions. *Drug Information Journal, 19,* 305-317.

Gandhi, T.K., Burstin, H., Cook, E.F., Puopolo, A.L., Haas, J.S., Brennan, T.A. et al. (2000). Drug complications in outpatients. *Journal of General Internal Medicine, 15,* 149-154.

Gandhi, T.K., Seger, D.L., & Bates, D.W. (2000). Identifying drug safety issues: from research to practice. *International Journal for Quality in Health Care, 12,* 69-76.

Garnett, W. & Dukes, G. (1988). Upper gastrointestinal disorders. In L.Young & M. Koda-Kimble (Eds.), *Applied Therapeutics: The Clinical Use of Drugs* (4th ed., pp. 447-465). Vancouver WA: Applied Therapeutics, Inc.

Gibson, G.A. (2000). Economic and humanistic impact of adverse events associated with CSFs. *Pharmacotherapy, 20,* 118S-120S.

Girard, M. (1984). Testing the methods of assessment for adverse drug reactions. *Adverse Drug Reactions & Acute Poisoning Reviews, 4,* 234-244.

Gordon, A.J. (1985). Numerators, denominators, and other holy grails: management and interpretation of worldwide drug safety data. *Drug Information Journal, 19,* 319-328.

Gray, S.L., Mahoney, J.E., & Blough, D.K. (1999). Adverse drug events in elderly patients receiving home health services following hospital discharge. *Annals of Pharmacotherapy, 33,* 1147-1153.

Gray, T.K., Adams, L.L., & Fallon, H.J. (1973). Short-term intense surveillance of adverse drug reactions. *Journal of Clinical Pharmacology, 13,* 61-67.

Green, C.F., Mottram, D.R., Rowe, P.H., & Pirmohamed, M. (2000). Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. *Journal of Clinical Pharmacy and Therapeutics, 25,* 355-361.

Green, D.M. (1964). Pre-existing conditions, placebo reactions, and "side effects". *Annals of Internal Medicine, 60,* 255-265.

Grymonpre, R.E., Mitenko, P.A., Sitar, D.S., Aoki, F.Y., & Montgomery, P.R. (1988). Drug-associated hospital admissions in older medical patients. *Journal of the American Geriatric Society, 36,* 1092-1098.

Hallas, J., Gram, L.F., Grodum, E., Damsbo, N., Brosen, K., Haghfelt, T. et al. (1992). Drug related admissions to medical wards: a population based survey. *British Journal of Clinical Pharmacology, 33,* 61-68.

Hamilton, R.A., Briceland, L.L., & Andritz, M.H. (1998). Frequency of hospitalization after exposure to known drug-drug interactions in a medicaid population. *Pharmacotherapy, 18,* 1112-1120.

Hanlon, J.T., Schmader, K.E., Koronkowski, M.J., Weinberger, M., Landsman, P.B., Samsa, G.P. et al. (1997). Adverse drug events in high risk older outpatients. *Journal of the American Geriatric Society, 45,* 945-948.

Harris, R.Z., Benet, L.Z., & Schwartz, J.B. (1995). Gender effects in pharmacokinetics and pharmacodynamics. *Drugs, 50,* 222-239.

Health Care Financing Administration (2001). *International Classification of Diseases, 9th Revision, Clinical Modification.* (6th ed.) Los Angeles: Practice Management Information Corporation.

Hennekens, C.H. & Buring, J.E. (1987a). Case-control studies. In S.L.Mayrent (Ed.), *Epidemiology in Medicine* (1 ed., pp. 132-152). Boston: Little, Brown and Company.

Hennekens, C.H. & Buring, J.E. (1987b). Evaluating the role of confounding. In S.L.Mayrent (Ed.), *Epidemiology in Medicine* (1st ed., pp. 287-323). Boston: Little, Brown and Company.

Hennekens, C.H. & Buring, J.E. (1987c). Statistical association and cause-effect relationships. In S.L.Mayrent (Ed.), *Epidemiology in Medicine* (1st ed., pp. 30-53). Boston: Little, Brown and Company.

Honigman, B., Lee, J., Rothschild, J., Light, P., Pulling, R.M., Yu, T. et al. (2001). Using computerized data to identify adverse drug events in outpatients. *Journal of American Medical Information Association, 8,* 254-266.

Honigman, B., Light, P., Pulling, R.M., & Bates, D.W. (2001). A computerized method for identifying incidents associated with adverse drug events in outpatients. *International Journal of Medical Information, 61,* 21-32.

Hosmer, D.W. & Lemeshow, S. (1989). Assessing the fit of the model. In *Applied Logistic Regression* (pp. 135-175). New York: Jon Wiley & Sons.

Hurwitz, N. (1969a). Admissions to hospital due to drugs. *British Medical Journal, 1,* 539-540.

Hurwitz, N. (1969b). Predisposing factors in adverse reactions to drugs. *British Medical Journal, 1,* 536-539.

Hurwitz, N. & Wade, O.L. (1969). Intensive hospital monitoring of adverse reactions to drugs. *British Medical Journal, 1,* 531-536.

Hutchinson, T.A., Flegel, K.M., Kramer, M.S., Leduc, D.G., & Ho Ping Kong, H. (1986). Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective study. *Journal of Chronic Diseases, 39,* 533-542.

Hutchinson, T.A. & Lane, D.A. (1989). Assessing methods for causality assessment of suspected adverse drug reactions. *Journal of Clinical Epidemiology, 42,* 5-16.

Hutchinson, T.A., Leventhal, J.M., Kramer, M.S., Karch, F.E., Lipman, A.G., & Feinstein, A.R. (1979). An algorithm for the operational assessment of adverse drug reactions. II. Demonstration of reproducibility and validity. *Journal of the American Medical Association, 242,* 633-638.

Ibanez, L., Laporte, J.R., & Carne, X. (1991). Adverse drug reactions leading to hospital admission. *Drug Safety, 6,* 450-459.

Iezzoni LI (1997). Data sources and implications: administrative databases. In L.I.Iezzoni (Ed.), *Risk Adjustment for Measuring Healthcare Outcomes* (2nd ed., pp. 169-242). Chicago: Health Administration Press.

Iezzoni, L.I., Foley, S.M., Daley, J., Hughes, J., Fisher, E.S., & Heeren, T. (1992). Comorbidities, complications, and coding bias. Does the number of diagnosis codes matter in predicting in-hospital mortality? *Journal of the American Medical Association, 267,* 2197-2203.

Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C., & Bonati, M. (2001). Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *British Journal of Clinical Pharmacology, 52,* 77-83.

Ives, T.J., Bentz, E.J., & Gwyther, R.E. (1987). Drug-related admissions to a family medicine inpatient service. *Archives of Internal Medicine, 147,* 1117-1120.

Jankel, C.A. & Fitterman, L.K. (1993). Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Safety, 9,* 51-59.

Jick, H. (1974). Drugs -- remarkably nontoxic. *New England Journal of Medicine, 291,* 824-828.

Jick, H. & Brandt, D.E. (1984). Allopurinol and cataracts. *American Journal of Ophthalmology, 98,* 355-358.

Jick, H., Jick, S.S., & Derby, L.E. (1991). Validation of information recorded on general practitioner based computerized data resource in the United Kingdom. *British Medical Journal, 302,* 766-768.

Jick, H. & Walker, A.M. (1989). Uninformed criticism of automated record linkage. *Clinical Pharmacology & Therapeutics, 46,* 478-479.

Johnson, J.A. & Bootman, J.L. (1995). Drug-related morbidity and mortality: a cost-of-illness model. *Archives of Internal Medicine, 155,* 1949-1956.

Jones, J.K. (1982). Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. *Family & Community Health, 5,* 58-67.

Karch, F.E. & Lasagna, L. (1975). Adverse drug reactions: a critical review. *Journal of the American Medical Association, 234,* 1236-1241.

Karch, F.E., Smith, C.L., Kerzner, B., Mazzullo, J.M., Weintraub, M., & Lasagna, L. (1976). Adverse drug reactions--a matter of opinion. *Clinical Pharmacology & Therapeutics, 19,* 489-492.

Kellaway, G.S.M. & McCrae, E. (1973). Intensive monitoring for adverse drug effects in patients discharged from acute medical wards. *New Zealand Medical Journal, 78,* 525-528.

Kelly, W.N. (2001a). Potential risks and prevention, part 1: fatal adverse drug events. *American Journal of Health-System Pharmacy, 58,* 1317-1324.

Kelly, W.N. (2001b). Potential risks and prevention, part 2: drug-induced permanent disabilities. *American Journal of Health-System Pharmacy, 58,* 1325-1329.

King, M.A., Purdie, D.M., & Roberts, M.S. (2001). Matching prescription claims with medication data for nursing home residents: Implications for prescriber feedback, drug utilization studies and selection of prescription claims database. *Journal of Clinical Epidemiology, 54,* 202-209.

Klein, L.E., German, P.S., Levine, D.M., Feroli, E.R., & Ardery, J. (1984). Medication problems among outpatients. A study with emphasis on the elderly. *Archives of Internal Medicine, 144,* 1185-1188.

Klinker, K., Harbilas, J., & Johns, T. (2002). Drug-induced hematologic disorders. In J.DiPiro, R. Talbert, G. Yee, G. Matzke, B. Wells, & L. Posey (Eds.), *Pharmacotherapy: A Pathophysiologic Approach* (5th ed., pp. 1783-1795). New York: McGraw-Hill.

Knight, M. (1994). Adverse drug reactions in neonates. *Journal of Clinical Pharmacology, 34,* 128-135.

Koch-Weser, J. (1968). Definition and classification of adverse drug reactions. *Drug Information Bulletin, 2,* 72-78.

Koch-Weser, J., Sellers, E.M., & Zacest, R. (1977). The ambiguity of adverse drug reactions. *European Journal of Clinical Pharmacology, 11,* 75-78.

Koch-Weser, J., Sidel, V.W., Sweet, R.H., Kanarek, P., & Eaton, A.E. (1969). Factors determining physician reporting of adverse drug reactions. *New England Journal of Medicine, 280,* 20-26.

Koecheler Schneider, J., Mion, L.C., & Frengley, J.D. (1992). Adverse drug reactions in an elderly outpatient population. *American Journal of Hospital Pharmacy, 49,* 90-96.

Kohler, G.I., Bode-Boger, S.M., Busse, R., Hoopmann, M., Welte, T., & Boger, R.H. (2000). Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *International Journal of Clinical Pharmacology & Therapeutics, 38,* 504-513.

Kramer, M.S., Hutchinson, T.A., Flegel, K.M., Naimark, L., Contardi, R., & Leduc, D.G. (1985). Adverse drug reactions in general pediatric outpatients. *Journal of Pediatrics, 106,* 305-310.

Kramer, M.S., Leventhal, J.M., Hutchinson, T.A., & Feinstein, A.R. (1979). An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *Journal of the American Medical Association, 242,* 623-632.

Kroenke, K. (1985). Polypharmacy: causes, consequences, and cure. *American Journal of Medicine, 79,* 149-152.

Lacoste-Roussillon, C., Pouyanne, P., Haramburu, F., Miremoint, G., & Begaud, B. (2001). Incidence of serious adverse drug reactions in general practice: a prospective study. *Clinical Pharmacology & Therapeutics, 69,* 458-462.

Lagnaoui, R., Moore, N., Fach, J., Longy-Boursier, M., & Begaud, B. (2000). Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *European Journal of Clinical Pharmacology, 55,* 181-186.

Lakshmanan, M.C., Hershey, C.O., & Breslau, D. (1986). Hospital admissions caused by iatrogenic disease. *Archives of Internal Medicine, 146,* 1931-1934.

Lamberg, S. (2002). *Blackwell's Primary Care Essentials: Dermatology.* (2nd ed.) Malden MA: Blackwell Science.

Larmour, I., Dolphin, R.G., Baxter, H., Morrison, S., Hooke, D.H., & McGrath, B.P. (1991). A prospective study of hospital admissions due to drug reactions. *Australian Journal of Hospital Pharmacy, 21,* 90-95.

Lau, H.S., deBoer, A., Beuning, K.S., & Porsius, A. (1997). Validation of pharmacy records in drug exposure assessment. *Journal of Clinical Epidemiology, 50,* 619-625.

Lazarou, J., Pomeranz, B.H., & Corey, P.N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Journal of the American Medical Association, 279,* 1200-1205.

Leach, S. & Roy, S.S. (1986). Adverse drug reactions: an investigation on an acute geriatric ward. *Age and Ageing, 15,* 241-246.

Leape, L.L. (1999). Why should we report adverse incidents? *Journal of Evaluation in Clinical Practice, 5,* 1-4.

Leape, L.L., Brennan, T.A., Laird, N., Lawthers, A.G., Localio, A.R., Barnes, B.A. et al. (1991). The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *New England Journal of Medicine, 324,* 377-384.

Lee, A., Rawlins, M.D., & Smith, J.M. (1992). A study of expert judgements on adverse drug reaction reports, and comparison with algorithmic methods. *British Journal of Clinical Pharmacology, 34,* 157P.

Letrilliart, L., Hanslik, T., Biour, M., Fagot, J.P., Guiguet, M., & Flahault, A. (2001). Postdischarge adverse drug reactions in primary care originating from hospital care in France: a nationwide prospective study. *Drug Safety, 24,* 781-792.

Levy, M., Lipshitz, M., & Eliakim, M. (1979). Hospital admissions due to adverse drug reactions. *The American Journal of the Medical Sciences, 277,* 49-56.

Lewis, N.J.W., Patwell, J.T., & Briesacher, B.A. (1993). The role of insurance claims databases in drug therapy outcomes research. *Pharmacoeconomics, 4,* 323-330.

Liu, B.A., Knowles, S.R., Mittmann, N., Einarson, T., & Shear, N.H. (2001). Reporting of fatal adverse drug reactions. *Canadian Journal of Clinical Pharmacology, 8,* 84-88.

Lloyd, S.S. & Rissing, J.P. (1985). Physician and coding errors in patient records. *Journal of the American Medical Association, 254,* 1330-1336.

Lumley, C.E., Walker, S.R., Hall, G.C., Staunton, N., & Grob, P.R. (1986). The under-reporting of adverse drug reactions seen in general practice. *Pharmaceutical Medicine, 1,* 205-212.

Malhotra, S., Jain, S., & Pandhi, P. (2001). Drug-related visits to the medical emergency department: a prospective study from India. *International Journal of Clinical Pharmacology and Therapeutics, 39,* 12-18.

Manasse, H.R. (1989). Medication use in an imperfect world: drug misadventuring as an issue of public policy, part 1. *American Journal of Hospital Pharmacy, 46,* 929-944.

Mannesse, C.K., Derkx, F.H.M., deRidder, M.A.J., Man In 'T Veld', A.J., & van der Cammen, T.J.M. (2000). Contribution of adverse drug reactions to hospital admissions of older patients. *Age & Ageing, 29,* 35-39.

Mannesse, C.K., Derkx, F.H.M., deRidder, M.A.J., Man in't Veld, A.J., & van der Cammen, T.J.M. (1997). Adverse drug reactions in elderly patients as contributing factor for hospital admission: cross sectional study. *British Medical Journal, 315,* 1057-1058.

Martin, R.M., Biswas, P.N., Freemantle, S.N., Pearce, G.L., & Mann, R.D. (1998). Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *British Journal of Clinical Pharmacology, 46,* 505-511.

Martinez-Mir, I., Garcia-Lopez, M., Palop, V., Ferrer, J.M., Rubio, E., & Morales-Olivas, F.J. (1999). A prospective study of adverse drug reactions in hospitalized children. *British Journal of Clinical Pharmacology, 47,* 681-688.

Martys, C.R. (1979). Adverse reactions to drugs in general practice. *British Medical Journal, 2,* 1194-1197.

May, F.E., Stewart, R.B., & Cluff, L.E. (1977). Drug interactions and multiple drug administration. *Clinical Pharmacology & Therapeutics, 22,* 322-328.

McCarthy, E.P., Iezzoni, L.I., Davis, R.B., Palmer, R.H., Cahalane, M., Hamel, M.B. et al. (2000). Does clinical evidence support ICD-9-CM diagnosis coding of complications? *Medical Care, 38,* 868-876.

McKenney, J.M. & Harrison, W.L. (1976). Drug-related hospital admissions. *American Journal of Hospital Pharmacy, 33,* 792-795.

McKenzie, M.W., Stewart, R.B., Weiss, C.F., & Cluff, L.E. (1973). A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. *American Journal of Hospital Pharmacy, 30,* 898-903.

McLeod, P.J., Huang, A.R., Tamblyn, R.M., & Gayton, D.C. (1997). Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *Canadian Medical Association Journal, 156,* 385-391.

McMahon, L.F. & Smits, H.L. (1986). Can Medicare prospective payment survive the ICD-9-CM disease classification system? *Annals of Internal Medicine, 104,* 562-566.

Meleney, H.E. & Fraser, M.L. (1969). A retrospective study of drug usage and adverse drug reactions in hospital outpatients final report. *Drug Information Bulletin, 69,* 124-127.

Menniti-Ippolito, F., Raschetti, R., Da Cas, R., Giaquinto, C., & Cantarutti, L. (2000). Active monitoring of adverse drug reactions in children. *Lancet, 355,* 1613-1614.

Methodologist's Toolchest (2000). Methodologist's Toolchest 3.0 [Computer software]. Thousand Oaks, CA: Sage Publications.

Meyboom, R.H.B., Lindquist, M., Flygare, A.K., Biriell, C., & Edwards, I.R. (2000). The value of reporting therapeutic ineffectiveness as an adverse drug reaction. *Drug Safety, 23,* 95-99.

Meyer, U.A. (2000). Pharmacogenetics and adverse drug reactions. *Lancet, 356,* 1667-1671.

Michel, D.J. & Knodel, L.C. (1986). Comparison of three algorithms used to evaluate adverse drug reactions. *American Journal of Hospital Pharmacy, 43,* 1709-1714.

Millar, J.S. (2001). Consultations owing to adverse drug reactions in a single practice. *British Journal of General Practice, 51,* 130-131.

Miller, E., Blatman, B., & Einarson, T.R. (1996). A survey of population-based drug databases in Canada. *Canadian Medical Association Journal, 154,* 1855-1864.

Miller, R.R. (1974). Hospital admissions due to adverse drug reactions: a report from the Boston collaborative drug surveillance program. *Archives of Internal Medicine, 134,* 219-223.

Mitchell, A.A., Lacouture, P.G., Sheehan, J.E., Kauffman, R.E., & Shapiro, S. (1988). Adverse drug reactions in children leading to hospital admission. *Pediatrics, 82,* 24-29.

Moore, D. (2002a). Delirium, dementia, and related disorders. In *Psychiatry* (2nd ed., pp. 57-94). Malden MA: Blackwell Sciences.

Moore, D. (2002b). Schizophrenia and other psychoses. In *Psychiatry* (2nd ed., pp. 122-144). Malden MA: Blackwell Sciences.

Moore, N. (2001). The role of the clinical pharmacologist in the management of adverse drug reactions. *Drug Safety, 24,* 1-7.

Moore, N., Lecointre, D., Noblet, C., & Mabille, M. (1998). Frequency and cost of serious adverse drug reactions in a department of general medicine. *British Journal of Clinical Pharmacology, 45,* 301-308.

Moore, T.J., Psaty, B.M., & Furberg, C.D. (1998). Time to act on drug safety. *Journal of the American Medical Association, 279,* 1571-1573.

Motheral, B.R. & Fairman, K.A. (1997). The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical Therapeutics, 19,* 346-366.

Mulroy, R. (1973). Iatrogenic disease in general practice: its incidence and effects. *British Medical Journal, 2,* 407-410.

Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A. et al. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics, 30,* 239-245.

Naranjo, C.A., Shear, N.H., & Lanctot, K.L. (1992). Advances in the diagnosis of adverse drug reactions. *Journal of Clinical Pharmacology, 32,* 897-904.

Nelson, K.M. & Talbert, R.L. (1996). Drug-related hospital admissions. *Pharmacotherapy, 16,* 701-707.

Nelson, M., Berchou, R., & LeWitt, P. (2002). Parkinson's disease. In J.DiPiro, R. Talbert, G. Yee, G. Matzke, B. Wells, & L. Posey (Eds.), *Pharmacotherapy: A Pathophysiologic Approach* (5th ed., pp. 1089-1102). New York: McGraw-Hill.

Newman, T.B., Browner, W.S., Cummings, S.R., & Hulley, S.B. (2001). Designing an observational study: cross-sectional and case-control studies. In S.B.Hulley, S. R. Cummings, W. S. Browner, D. Grady, N. Hearst, & T. B. Newman (Eds.), *Designing Clinical Research* (2nd ed., pp. 107-123). Philadelphia: Lippincott Williams & Wilkins.

Ninno, S.D. & Ninno, M.A. (2002). Adverse drug events. In B.A.Mueller, K. E. Bertch, T. S. Dunsworth, S. C. Fagan, M. S. Hayney, M. B. O'Connell, G. T. Schumock, D. F. Thompson, J. E. Tisdale, D. M. Witt, & B. J. Zarowitz (Eds.), *The Science and Practice of Pharmacotherapy I and II* (4th ed., pp. 111-146). Kansas City: American College of Clinical Pharmacy.

Nolan, L. & O'Malley, K. (1988). Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions. *Journal of the American Geriatric Society, 36,* 142-149.

Norman, G.R. & Streiner, D.L. (2000). Multiple regression. In *Biostatistics: The Bare Essentials* (2nd ed., pp. 127-138). Hamilton Ontario: B.C. Decker Inc.

O'Hara, D.A. & Carson, N.J. (1997). Reporting of adverse events in hospitals in Victoria, 1994-1995. *Medical Journal of Australia, 166,* 460-463.

O'Neil, A.C., Petersen, L.A., Cook, E.F., Bates, D.W., Lee, T.H., & Brennan, T.A. (1993). Physician reporting compared with medical-record review to identify adverse medical events. *Annals of Internal Medicine, 119,* 370-376.

Pirmohamed, M., Breckenridge, A.M., Kitteringham, N.R., & Park, B.K. (1998). Fortnightly review: adverse drug reactions. *British Medical Journal, 316,* 1295-1298.

Pouyanne, P., Haramburu, F., Imbs, J.L., & Begaud, B. (2000). Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. *British Medical Journal, 320,* 1036.

Prince, B.S., Goetz, C.M., Rihn, T.L., & Olsky, M. (1992). Drug-related emergency department visits and hospital admissions. *American Journal of Hospital Pharmacy, 49,* 1696-1700.

Quam, L., Ellis, L.B.M., Venus, P., Clouse, J., Taylor, C.G., & Leatherman, S. (1993). Using claims data for epidemiologic research. *Medical Care, 31,* 498-507.

Rademaker, M. (2001). Do women have more adverse drug reactions? *American Journal of Clinical Dermatology, 2,* 349-351.

Rawlins, M.D. (1995). Pharmacovigilance: paradise lost, regained or postponed? The William Withering Lecture 1994. *Journal of the Royal College of Physicians of London, 29,* 41-49.

Ray, W.A., Griffin, M.R., Schaffner, W., Baugh, D.K., & Melton, L.J. (1987). Psychotropic drug use and the risk of hip fracture. *New England Journal of Medicine, 316,* 363-369.

Reidenberg, M.M. & Lowenthal, D.T. (1968). Adverse nondrug reactions. *New England Journal of Medicine, 279,* 678-679.

Rosner, B. (2000). Design and analysis techniques for epidemiologic studies. In *Fundamentals of Biostatistics* (5th ed., pp. 577-676). Pacific Grove: Duxbury.

Roughead, E.E. (1999). The nature and extent of drug-related hospitalisations in Australia. *Journal of Quality in Clinical Practice, 19,* 19-22.

Royer, R.J. (1997). Mechanism of action of adverse drug reactions: an overview. *Pharmacoepidemiology and Drug Safety, 6,* S43-S50.

Sachs, R.M. & Bortnichak, E.A. (1986). An evaluation of spontaneous adverse drug reaction monitoring systems. *American Journal of Medicine, 81,* 49-55.

Saltsman, C.L. & Hamilton, R.A. (1999). Risk factors for patient hospitalization. *American Journal of Health-System Pharmacy, 56,* 453.

Schneitman McIntire, O., Farnen, T.A., Gordon, N., Chan, J., & Toy, W.A. (1996). Medication misadventures resulting in emergency department visits at an HMO medical center. *American Journal of Health-System Pharmacy, 53,* 1416-1422.

Schumock, G.T., Thornton, J.P., & Witte, K.W. (1991). Comparison of pharmacy-based concurrent surveillance and medical record retrospective reporting of adverse drug reactions. *American Journal of Hospital Pharmacy, 48,* 1974-1976.

Seeger, J.D., Kong, S.X., & Schumock, G.T. (1998). Characteristics associated with ability to prevent adverse drug reactions in hospitalized patients. *Pharmacotherapy, 18,* 1284-1289.

Shapiro, S. (1989). The role of automated record linkage in the postmarketing surveillance of drug safety: a critique. *Clinical Pharmacology & Therapeutics, 46,* 371-386.

Smith Rogers, A., Israel, E., Smith, C.R., Levine, D., McBean, A.M., Valente, C. et al. (1988). Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Archives of Internal Medicine, 148,* 1596-1600.

Smith, J.W., Seidl, L.G., & Cluff, L.E. (1966). Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. *Annals of Internal Medicine, 65,* 629-640.

Stephens, M.D.B. (1987). The diagnosis of adverse medical events associated with drug treatment. *Adverse Drug Reactions & Acute Poisoning Reviews, 1,* 1-35.

Steven, I.D., Malpass, A., Moller, J., Runciman, W.B., & Helps, S.C. (1999). Towards safer drug use in general practice. *Journal of Quality in Clinical Practice, 19,* 47-50.

Stoukides, C.A., D'Agostino, P.R., & Kaufman, M.B. (1993). Adverse drug reaction surveillance in an emergency room. *American Journal of Hospital Pharmacy, 50,* 712-714.

Strom, B.L. (1989). Automated data bases used for pharmacoepidemiology research. *Clinical Therapeutics, 46,* 390-394.

Strom, B.L. & Carson, J.L. (1990). Use of automated databases for pharmacoepidemiology research. *Epidemiologic Reviews, 12,* 87-107.

Strom, B.L. & Tugwell, P. (1990). Pharmacoepidemiology: current status, prospects, and problems. *Annals of Internal Medicine, 113,* 179-181.

Suh, D.C., Woodall, B.S., Shin, S.K., & Hermes-De Santis, E.R. (2000). Clinical and economic impact of adverse drug reactions in hospitalized patients. *Annals of Pharmacotherapy, 34,* 1373-1379.

Svarstad, B.L., Cleary, P.D., Mechanic, D., & Robers, P.A. (1987). Gender differences in the acquisition of prescribed drugs: an epidemiological study. *Medical Care, 25,* 1089-1098.

Tabachnick, B.G. & Fidell, L.S. (2001a). Logistic regression. In R.Pascal (Ed.), *Using Multivariate Statistics* (4th ed., pp. 517-581). Needham Heights MA: Allyn & Bacon.

Tabachnick, B.G. & Fidell, L.S. (2001b). Multiple regression. In R.Pascal (Ed.), *Using Multivariate Statistics* (4th ed., pp. 111-176). Needham Heights MA: Allyn & Bacon.

Tafreshi, M.J., Melby, M.J., Kaback, K.R., & Nord, T.C. (1999). Medication-related visits to the emergency department: a prospective study. *Annals of Pharmacotherapy, 33,* 1252-1257.

Tamblyn, R., Lavoie, G., Petrella, L., & Monette, J. (1995). The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. *Journal of Clinical Epidemiology, 48,* 999-1009.

Tamblyn, R., McLeod, P.J., Abrahamowicz, M., & Laprise, R. (1996). Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *Canadian Medical Association Journal, 154,* 1177-1184.

Tran, C., Knowles, S.R., Liu, B.A., & Shear, N.H. (1998). Gender differences in adverse drug reactions. *Journal of Clinical Pharmacology, 38,* 1003-1009.

TRICARE Management Activity (2002a). Pharmacy co-pays. Retrieved on 4-11-2002a, http://www.tricare.osd.mil/pharmacy/newcopay.cfm.

TRICARE Management Activity (2002b). TRICARE regions at a glance. Retrieved on 4-11-0002b, http://www.tricare.osd.mil/regionalinfo/.

TRICARE Support Office (1997). *TRICARE standard handbook.* Aurora CO: TRICARE Support Office.

van Eijk, M.E.C., Krist, L.F.G., Avorn, J., Porsius, A., & de Boer, A. (2001). Do the research goal and databases match? A checklist for a systematic approach. *Health Policy, 58,* 263-274.

Veehof, L.J.G., Stewart, R.E., Meyboom-de Jong, B., & Haaijer-Ruskamp, F.M. (1999). Adverse drug reactions and polypharmacy in the elderly in general practice. *European Journal of Clinical Pharmacology, 55,* 533-536.

Venulet, J. & Ten Ham, M. (1996). Methods for monitoring and documenting adverse drug reactions. *International Journal of Clinical Pharmacology & Therapeutics, 34,* 112-129.

Von Korff, M., Wagner, E.H., & Saunders, K. (1992). A chronic disease score from automated pharmacy data. *Journal of Clinical Epidemiology, 45,* 197-203.

Waller, P.C. (1992). Measuring the frequency of adverse drug reactions. *British Journal of Clinical Pharmacology, 33,* 249-252.

Waller, P.C. (1994). Dealing with variability: the role of pharmacovigilance. *Journal of Pharmacy & Pharmacology, 46,* 445-449.

West, S.L., Savitz, D.A., Koch, G., Strom, B.L., Guess, H.A., & Hartzema, A. (1995). Recall accuracy for prescription medications: self-report compared with database information. *American Journal of Epidemiololgy, 142,* 1103-1112.

Whipple, J.K., Ausman, R.K., & Quebbeman, E.J. (1992). Narcotic use in the hospital: reasonably safe? *Annals of Pharmacotherapy, 26,* 897-901.

White, T.J., Arakelian, A., & Rho, J.P. (1999). Counting the costs of drug-related adverse events. *Pharmacoeconomics, 15,* 445-458.

WHO Collaborating Centre for International Drug Monitoring (2002). Uppsala monitoring centre - definitions. Accessed on 4-11-2002, www.who-umc.org/defs.html.

Willcox, S.M., Himmelstein, D.U., & Woolhandler, S. (1994). Inappropriate drug prescribing for the community-dwelling elderly. *Journal of the American Medical Association, 272,* 292-296.

Williamson, J. & Chopin, J.M. (1980). Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. *Age and Ageing, 9,* 73-80.

World Health Organization (1970). International drug monitoring--the role of the hospital--a WHO report. *Drug Intelligence & Clinical Pharmacy, 4,* 101-110.

Yosselson-Superstine, S. & Weiss, T. (1982). Drug-related hospitalization in paediatric patients. *Journal of Clinical & Hospital Pharmacy, 7,* 195-203.

Young, L.R., Wurtzbacher, J.D., & Blankenship, C.S. (1997). Adverse drug reactions: a review for healthcare practitioners. *The American Journal of Managed Care, 3,* 1884-1906.